501. *The Mixed Condensation of Ketones in the Presence of Methylanilinomagnesium Bromide.*

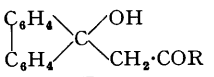
By W. D. GARDEN and F. D. GUNSTONE.

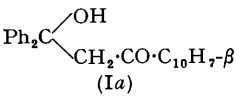
Fluorenone has been condensed with a number of ketones (mainly of the type COArMe) in good yield. The resulting ketols have been converted into various related products.

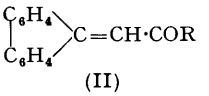
INTERACTION between a carbonyl group and an activated methylene group is the basis of versatile and important condensations (Hauser and Renfrow, *J. Amer. Chem. Soc.*, 1937, **59**, 1823 and many later papers), frequently of self-condensation of ketones but less often condensation of two different ketones (Wallach, *Ber.*, 1896, **29**, 1595, 2955; *Annalen*, 1912, **394**, 362; Ekeley and Carpenter, *J. Amer. Chem. Soc.*, 1926, **48**, 2375; Stevens, *ibid.*, 1934, **56**, 450; Voitila, *Suomen Kemistilehti*, 1936, **9**, *B*, 30; *Chem. Abstr.*, 1937, **31**, 2582; Colonge, *Bull. Soc. chim.*, 1934, **1**, 1101). The last author used methylanilinomagnesium bromide as condensing agent and described some mixed condensations in which one of the ketones (fluorenone or benzophenone) did not contain an enolisable hydrogen atom and thus could not react with itself. In this way the difficulty of the large number of possible products was partially overcome. This reagent has since been used with effect several times (Aksenova, *Chem. Abstr.*, 1941, **35**, 6238; Iwanow and Iwanow, *Ber.*, 1943, **76**, 988; Stoll and Rouvé, *Helv. Chim. Acta*, 1947, **30**, 2019; Friedman and Robinson, *Chem. and Ind.*, 1951, 777; Nielson, Gibbons, and Zimmermann, *J. Amer. Chem. Soc.*, 1951, **73**, 4696).

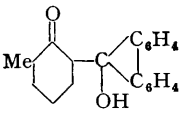
For the condensation of fluorenone with acetophenone by Colonge's method we recommend (*a*) that a 25% excess of condensing agent be used and (*b*) that condensation be effected in an atmosphere of nitrogen (which leads to less coloured products). We have thus condensed fluorenone with methyl α- and β-naphthyl ketones, *o*-chloro- and *p*-nitroacetophenone, 2-methyl*cyclo*hexanone, and α-tetralone, and benzophenone with α-tetralone and with methyl β-naphthyl ketone. The products are the expected ketols (I; R = α- and β-$C_{10}H_7$, *p*-$NO_2 \cdot C_6H_4$; and I*a*), except in two cases when the unsaturated ketones (II; R =

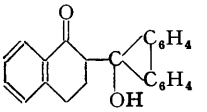
o-C_6H_4Cl) and (V) result directly. 2-Methyl*cyclo*hexanone is believed to condense in the 6-position (III) as the ketol has been converted into an unsaturated ketone; and α-tetralone probably condenses in the 2-position (IV and V) (cf. Elsevier's " Encyclopædia of Organic Chemistry," Series III, Vol. 12, *B*, pp. 2611—2613) though the 4-position is not ruled out. Benzil and acetophenone and fluorenone and *cyclo*hexanone have been condensed less satisfactorily. In addition we have been unable to condense fluorenone with deoxybenzoin, dibenzyl ketone, benzyl methyl ketone, propiophenone, butyrophenone, β-tetralone, benzylideneacetone, benzylacetone, diethyl ketone, or acetone, or anthraquinone or phenanthraquinone with *o*-chloroacetophenone. Condensation by Colonge's method appears to be limited almost entirely to ketones of the type COArMe, but yields are generally good when condensation does occur.

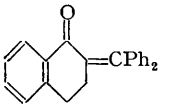

(I)


(Ia)


(II)


(III)

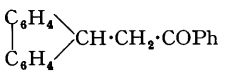

(IV)

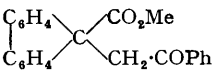

(V)

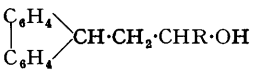
The method is obviously only of value in the preparation of a few ketols and attention was directed toward the possible uses of such products as were obtained. Treatment with acid under appropriate conditions converts the ketols into the corresponding αβ-unsaturated ketones (II), whilst the saturated ketones (*e.g.*, VI) are easily obtained by reaction with hydrogen iodide.

Attempts to oxidise 9-phenacylfluorene (VI) to the diketone by selenium dioxide (Riley, Morley, and Friend, *J.*, 1932, 1875; Waitkins and Clark, *Chem. Reviews*, 1945, **36**, 235; Rabjohn, *Org. Reactions*, **5**, 331) were unsuccessful. The ketone was either recovered unchanged or the unsaturated ketone (II; R = Ph) was obtained (cf. Astin, Newman, and Riley, *J.*, 1933, 391; Armstrong and Robinson, *J.*, 1934, 1650). Methyl 9-phenacylfluorene-9-carboxylate (VII) which is readily hydrolysed to (VI), was prepared following Wislicenus and Mocker (*Ber.*, 1913, **46**, 2791); but this also was not oxidised by selenium dioxide.

Catalytic reduction of the appropriate ketone yielded the carbinol (VIII; R = Ph. α- or β-$C_{10}H_7$).


(VI)


(VII)


(VIII)

In presence of the condensing agent described by Weizmann (B.P. 582,191; *Chem. Abstr.*, 1947, **41**, 2436)—potassium hydroxide in an acetal—fluorenone condensed directly with two molecules of acetophenone to give, probably, diphenacylfluorene (Dufraisse and de Carvalho, *Bull. Soc. chim.*, 1936, **3**, 882), which could result from the Michael addition of a second molecule of acetophenone to the unsaturated ketone (II; R = Ph). Fluorenone could not be made to condense with propiophenone or dypnone by this method.

Experimental

Condensation of Fluorenone and Acetophenone.—Magnesium (1·0 g., 0·041 mole) was placed in a three-necked flask (250 ml.) fitted with reflux condenser ($CaCl_2$ drying tube), mercury-sealed stirrer, and dropping funnel, and the apparatus flushed out, through the condenser, with nitrogen. Ethylmagnesium bromide was prepared in the usual way from ethyl bromide (3·2 ml., 0·044 mole) in dry ether (7 ml.), with water-cooling as soon as the reaction began. [Under these conditions the Grignard compound was formed in *ca.* 85% yield as determined by Gilman's method (Gilman, Wilkinson, Fishel, and Meyers, *J. Amer. Chem. Soc.*, 1923, **45**, 156) and these

quantities thus give 25% excess of methylanilinomagnesium bromide if reaction with methylaniline is quantitative.] After the mixture had been stirred for 15 minutes a solution of methylaniline (3·75 g., 0·035 mole) in benzene (16 ml.) was rapidly added, ethane being evolved. The cooling bath was removed and fluorenone (5·06 g., 0·028 mole) in benzene (30 ml.) added. The temperature rose and a buff-coloured precipitate quickly separated. The mixture was stirred for 25 minutes, during which it cooled to room temperature. Then a mixture of benzene (25 ml.) and acetophenone (3·38 g., 0·028 mole) was added during 3 hours, after which the mixture was set aside overnight. Concentrated hydrochloric acid (8·0 ml., *ca.* 0·1 mole) and water (25 ml.) were then gradually added with ice-cooling, the benzene layer was separated and dried, and the solvent removed at $<45°$. The solid residue of 9-hydroxy-9-phenacylfluorene (I; R = Ph) crystallised from ethanol as colourless needles (7·18 g., 85%), m. p. 111—112° raised to 112—113° after a further crystallisation from ethanol (Colonge, *loc. cit.*, gives m. p. 112°).

Lower yields (40—75%) resulted when (*a*) the proportion of methylanilinomagnesium bromide, (*b*) the temperature at which the reactants were added, (*c*) the time for which the complex of fluorenone and condensing agent was stirred, or (*d*) the time for which the final mixture was kept varied from the conditions described above.

In subsequent condensations the molar proportions of reagents used and the method were as given above unless otherwise stated. The ketones used were either commercially available or prepared by known methods.

Attempts to separate 9-hydroxy-9-phenacylfluorene from its parent ketones by selective adsorption on acid-washed alumina, silica gel, or fuller's earth were unsuccessful, the alumina decomposing the ketol into its components. Nor could the αβ-unsaturated ketone derived from the ketol be separated from the two ketones by this method.

Other Condensations.—The products isolated are recorded in Table 1.

Condensation of Benzil and Acetophenone.—Condensation of benzil (3·0 g., 0·014 mole) with acetophenone (3·38 g., 0·027 mole) gave an unidentified substance (3·0 g.), m. p. 175° (yellow prisms from acetonitrile), unchanged by treatment with dry hydrogen chloride in acetic acid (Found: C, 85·9; H, 6·5%; *M*, cryoscopic in benzene, 293).

Condensation of Fluorenone and cyclo*Hexanone.*—No solid was obtained except in one experiment when a little high-melting *substance* resulted (m. p. 193—194° from ethyl acetate) which is probably a condensation product of *cyclo*hexanone with two molecules of fluorenone (Found: C, 84·0; H, 5·5. $C_{32}H_{26}O_3$ requires C, 83·8; H, 5·7%).

Effect of Temperature on the Reaction Product.—Fluorenone was condensed with methyl α-naphthyl ketone, the recommended procedure being varied by adding the latter ketone to the reaction mixture at various temperatures. The product was a mixture of ketol and unsaturated ketone easily separable by crystallisation from benzene from which the former crystallises more readily. The results given below indicate that greater yields of a mixed product may be obtained at higher temperatures than that already suggested.

Reaction temp.	15°	35°	45°	54°	70°	reflux
Ketol, %	59	54	44	25	13	nil
Unsaturated ketone, %	nil	11	17	51	41	62

Conversion of Ketols into αβ-Unsaturated Ketones.—Dehydration was effected under acid conditions but no method was found to give optimum conditions for all ketols. The following procedures were used:

(i) Refluxing in 96% formic acid solution (Colonge, *Bull. Soc. chim.*, 1935, **2**, 57).

(ii) Concentrated sulphuric acid (1 ml.) in acetic acid (6 ml.) was added to the ketol (1 g.) in the same solvent (20 ml.). After 30 minutes the product was isolated by dilution with water.

(iii) Dry hydrogen chloride was passed through a solution of ketol in acetic acid (quantities as above) for 20 minutes. The product was isolated by dilution with water after several hours.

(iv) The ketol (1 g.) was heated under reflux for 2 hours with benzene (25 ml.) and a little iodine, which was subsequently removed by sodium hydrogen sulphite solution, the product being isolated from the benzene layer.

The unsaturated ketones listed in Table 2 were prepared from the appropriate ketols.

Preparation of the Saturated Ketones.—The saturated ketones were obtained by boiling the ketol or unsaturated ketone (1 g.) in glacial acetic acid (8 ml.) with 55% hydrogen iodide (4 ml.) for 5 hours or 1 hour respectively. Reduction of the ketol may proceed *via* the unsaturated ketone since this compound results if the reaction period is too short. The reactants were then diluted with water, sodium hydrogen sulphite was added, and the ketone extracted with chloroform. The ketones described in Table 3 (all colourless needles) were thus prepared.

TABLE 1.

Product	Yield, % [1]	M. p.	Solvent [2]	Appearance	Found, % C	Found, % H	Formula	Required, % C	Required, % H
9-*Hydroxy*-9-*fluorenylmethyl α-naphthyl ketone* ...	60	137° *	EtOAc, MeCN	Colourless plates	85·5	5·1	$C_{25}H_{18}O_2$	85·7	5·2
9-*Hydroxy*-9-*fluorenylmethyl β-naphthyl ketone* ...	96	126—128*	C_6H_6, EtOH	Colourless needles	85·7	5·3	$C_{25}H_{18}O_2$	85·7	5·2
o-*Chlorophenacylidenefluorene* [3]	45	131	EtOH, MeCN	Orange needles	79·4	4·3	$C_{21}H_{13}OCl$	79·6	4·1
9-*Hydroxy*-9-p-*nitrophenacylfluorene*	45	134—135	AcOH, C_6H_6	Buff needles	73·3	4·3	$C_{21}H_{15}O_4N$ [4]	73·0	4·4
9-*Hydroxy*-9-(1 : 2 : 3 : 4-*tetrahydro*-1-*keto*-2-*naphthyl*)*fluorene*	84	135—136	C_6H_6, MeCN	Colourless needles	84·4	5·8	$C_{23}H_{18}O_2$	84·6	5·6
9-*Hydroxy*-9-(2-*keto*-3-*methyl*cyclo*hexyl*)*fluorene* ...	90	109—110	EtOH, C_6H_6–Pet.	Colourless plates	82·0	7·0	$C_{20}H_{20}O_2$	82·2	6·9
2-*Hydroxy*-2 : 2-*diphenylethyl β-naphthyl ketone* [5]	57	124—125	MeOH	—	—	—	$C_{25}H_{20}O_2$	—	—
2-*Diphenylmethylene*-α-*tetralone* [6]	21	206—207	EtOAc	Pale yellow needles	88·7	6·2	$C_{23}H_{18}O$	89·0	5·8

TABLE 2.

Unsaturated ketone	Method of dehydration	Yield, % [1]	M. p. (Solvent)	Appearance	Found, % C	Found, % H	Formula	Required, % C	Required, % H
9-Phenacylidenefluorene [7]	i	93	139° (EtOAc)	Orange polyhedra	—	—	$C_{21}H_{14}O$	—	—
9-*Fluorenylidenemethyl α-naphthyl ketone*	i	68	126—127 (MeCN)	Pale orange needles	90·4	5·1	$C_{25}H_{16}O$	90·3	4·9
	ii	86							
9-*Fluorenylidenemethyl β-naphthyl ketone*	iii	67	112—113 (MeCN)	Orange needles	90·5	5·1	$C_{25}H_{16}O$	90·3	4·9
9-p-*Nitrophenacylidenefluorene*	i	90	172 (AcOH)	Deep orange needles	77·1	3·6	$C_{21}H_{13}O_3N$ [8]	77·1	4·0
2-*Fluorenylidene*-α-*tetralone*	i	15	160 (AcOH)	Orange needles	89·6	5·4	$C_{23}H_{16}O$	89·6	5·2
	iii	10							
	iv	10							
β-*Naphthyl* 2 : 2-*diphenylvinyl ketone*	iii	48	167—168 (MeCN)	Pale brown polyhedra	89·7	5·3	$C_{25}H_{18}O$	89·8	5·4
9-(2-*Keto*-3-*methyl*cyclo*hexylidene*)*fluorene* [9] ...	iii	40	156—157 (EtOAc)	Yellow plates	87·5	6·6	$C_{20}H_{18}O$	87·6	6·6

TABLE 3.

Saturated ketone	Yield, % [1]	M. p. (Solvent)	Found, % C	Found, % H	Formula	Required, % C	Required, % H
9-Phenacylfluorene [10]	65	97 (EtOH)	—	—	$C_{21}H_{16}O$	—	—
9-*Fluorenylmethyl*-α-*naphthyl ketone*	82	164 (MeCN)	89·9	5·4	$C_{25}H_{18}O$	89·8	5·4
9-*Fluorenylmethyl β-naphthyl ketone*	67	107 (MeCN)	90·0	5·6	$C_{25}H_{18}O$	89·8	5·4
9-o-*Chlorophenacylfluorene*	70—80	109 (EtOH)	78·9	4·6	$C_{21}H_{15}OCl$ [11]	79·1	4·7
2-*Diphenylmethyl*-α-*tetralone*	58	147—148 (EtOH)	88·6	6·6	$C_{23}H_{20}O$	88·4	6·5

[1] The products obtained in these yields melted slightly lower than the figures quoted. [2] Where two solvents are quoted these were used separately in the order given. Pet. = light petroleum (b. p. 40—60°). [3] The liquid product solidified on trituration with light petroleum (b. p. 40—60°). The compound is unaffected by boiling 96% formic acid (Found : Cl, 11·3. Required : Cl, 11·2%). [4] Found : N, 4·0. Required : N, 4·1%. [5] This compound could not be purified as it decomposed with warm solvent but it was converted into the unsaturated ketone. [6] Purified by passage through a column of alumina; it was unaffected by hot formic acid. [7] Colonge (*loc. cit.*) gives m. p. 136—137°. [8] Found : N, 4·2. Required : N, 4·3%. [9] A small amount of a chlorine-containing compound was also obtained. [10] Wislicenus and Mocker (*loc. cit.*) give m. p. 96—97°; *oxime*, m. p. 160—161° (softens at 156°) (Found : C, 84·3; H, 5·7; N, 4·7. $C_{21}H_{17}ON$ requires C, 84·2; H, 5·7; N, 4·7%). [11] Found : Cl, 11·4. Required : Cl, 11·1%.
* With decomp.

Selenium Dioxide Oxidation of 9-Phenacylfluorene.—Attempts were made to oxidise 9-phenacylfluorene under various conditions. Oxidation was very slow and most of the starting material was recovered unchanged. By use of (i) aqueous acetic acid and (ii) aqueous 2-methoxyethanol containing four drops of 6N-hydrochloric acid, as solvent, however (Melnikov and Rokitsakja, *J. Gen. Chem. Russia*, 1944, **14**, 1054; Campbell and Khanna, *J.*, 1949, 533), good yields of 9-phenacylidenefluorene resulted.

Methyl 9-Phenacylfluorene-9-carboxylate (VII).—Methyl fluorene-9-carboxylate (3 g.) (Tucker, *J.*, 1949, 2182; Campbell and Tucker, *J.*, 1949, 2623) in methanol (10 ml.) was treated with sodium (0·3 g.) and, after 15 minutes, with phenacyl bromide (2·5 g.). The mixture was refluxed for 30 minutes, some of the solvent removed, and the product precipitated by dilution with water. Crystallisation from acetic acid gave *methyl 9-phenacylfluorene-9-carboxylate* (3·45 g., 68%), obtained as colourless plates, m. p. 177—179°, after further crystallisation (Found: C, 80·5; H, 5·4. $C_{23}H_{18}O_3$ requires C, 80·7; H, 5·3%). Treatment with alcoholic potassium hydroxide gave 9-phenacylfluorene, m. p. 94—96°. Attempts to oxidise (VII) with selenium dioxide gave only unchanged starting material.

9-(2-*Hydroxy*-2-*phenylethyl*)*fluorene* (VIII; R = Ph).—Catalytic hydrogenation (Raney nickel) of 9-phenacylfluorene dissolved in ethanol containing a trace of alkali, or of 9-phenacylidenefluorene suspended in the same solvent, yielded the *alcohol* as a colourless crystalline solid, m. p. 108—109° [from ethanol or from benzene–light petroleum (b. p. 40—60°)] (Found: C, 88·2; H, 6·3. $C_{21}H_{18}O$ requires C, 88·1; H, 6·3%); its 3:5-*dinitrobenzoate* formed yellow crystals [from benzene–light petroleum (b. p. 40—60°)], m. p. 198—200° (Found: C, 70·0; H, 4·4; N, 5·8. $C_{28}H_{20}O_6N_2$ requires C, 70·0; H, 4·2; N, 5·8%).

9-(2-*Hydroxy*-2-α- *and* -β-*naphthylethyl*)*fluorene.*—These alcohols were prepared from the saturated or unsaturated ketones as above. The α-*naphthyl* compound forms colourless crystals, m. p. 157—159°, from benzene (Found: C, 88·6; H, 5·8. $C_{25}H_{20}O$ requires C, 89·3; H, 6·0%), whilst the β-*isomer* is obtained as white spheres [from benzene–light petroleum (b. p. 40—60°)], m. p. 130—131·5° (Found: C, 89·2; H, 6·0%).

Condensation of Fluorenone with Acetophenone in the Presence of Potassium Hydroxide in Dipropoxyethane.—Vigorous stirring was maintained throughout this reaction. Potassium hydroxide (2·3 g., 0·041 mole) and dipropoxyethane (15 ml.) were slowly heated to 150° and then cooled to room temperature. The resulting condensing agent was cooled in ice during addition of fluorenone (5 g., 0·028 mole) and acetophenone (3·3 g., 0·028 mole) in dipropoxyethane (10 ml.) and for a further 20 minutes. Next morning water was added, a white solid being precipitated (2·53 g.). This crystallised readily from ethanol, acetic acid, or ethyl acetate. Crystallisation from the last solvent yielded, probably, 9:9-diphenacylfluorene, m. p. 200—202° (Dufraisse *et al.*, *loc. cit.*, give m. p. 203—204°) (Found: C, 86·7; H, 5·8. Calc. for $C_{29}H_{22}O_2$: C, 86·5; H, 5·5%).

We are indebted to the Department of Scientific and Industrial Research for a maintenance allowance to one of us (W. D. G.), and to Mr. J. M. L. Cameron and Miss R. H. Kennaway for the microanalyses.

UNIVERSITY OF GLASGOW. [*Received, April 4th*, 1952.]