Tetrahydropyranyl protecting group. II.[1] 3-Bromo-2-(tetrahydropyran-2-yloxy)-propene, a masked acetonyl bromide

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It is shown that the sodium hydride (in dimethyl formamide) induced elimination of hydrogen bromide from 1,3-dibromo-2-(tetrahydropyran-2-yloxy)propane (**3**) can be considered to result in the in situ formation of 3-bromo-2-(tetrahydropyran-2-yloxy)propene (**4**). When generated in this manner, **4** was shown to function as a masked acetonyl bromide of considerable utility. Under similar conditions, 1,3-dibromo-2-methoxypropane was assumed to produce 3-bromo-2-methoxypropene, which also was shown to be a useful masked acetonyl bromide.

The pyrolytic elimination of methanol from bromoacetone dimethyl ketal was shown to produce a 1:1 mixture of the two possible isomeric enol ethers, rather than pure 3-bromo-2-methoxypropene as stated in the literature (2).

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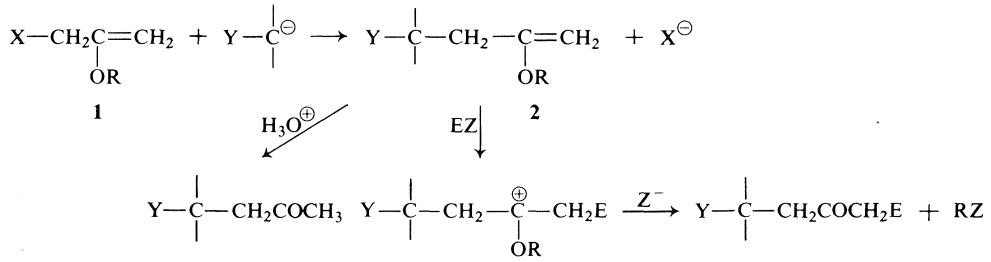
The introduction of an acetonyl moiety into a molecule possessing an activated methylene position is usually effected directly with acetonyl bromide (3) or acetonyl chloride (4). Alternatively, 2-step processes, involving alkylation with propargyl bromide followed by mercuric salt catalyzed hydration of the terminal acetylenic function (5), or, alkylation with 2,3-dichloropropene and subsequent hydrolysis of the vinylic chloride with concentrated sulfuric acid (6,7), are often used when the direct method is unsatisfactory. The great reactivity of bromo- and chloroacetone towards nucleophilic species reduces their usefulness as sources of the acetonyl group (e.g. a solution of the sodium salt of ethyl malonate in ethanol evidently gave only ethoxyacetone, see (4)), and the vigorous conditions necessary for the hydrolysis of the vinylic chloride often promote secondary reactions, such as cyclization and dehydration (see (7), for example), which limit the utility of the dichloropropene method. In contrast, the sequential introduction and hydration of a propargyl group at an activated methylene position is not subject to the above drawbacks, and consequently, this method is more widely applicable than the others.

In connection with various synthetic objectives, we required a masked acetonyl halide which retained the desirable characteristics of both 2,3-dichloropropene and the propargylic halides, and, in addition, had a proclivity to undergo substitution at the terminal carbon atom (C-3) subsequent to insertion at an activated (methylene) position. These requirements were likely to be met by a molecule which incorporated the functionalities of an allylic halide and an enol ether as in **1**. Hydrolysis of the alkylation product **2** obtained therefrom (eq. [1]), would unmask the acetonyl group, or electrophilic substitution of **2** could, at least in principle (8), result in the formation of an ω-substituted acetonyl moiety.

The tetrahydropyranyl ether **3** (eq. [2]), was chosen as a potential precursor of **1** (R = tetrahydropyran-2-yl) because of its ease of synthesis from commercially available, inexpensive starting materials. A solution of the dibromide **3** in anhydrous dimethyl formamide (DMF) containing an excess of sodium hydride was stable

[1]



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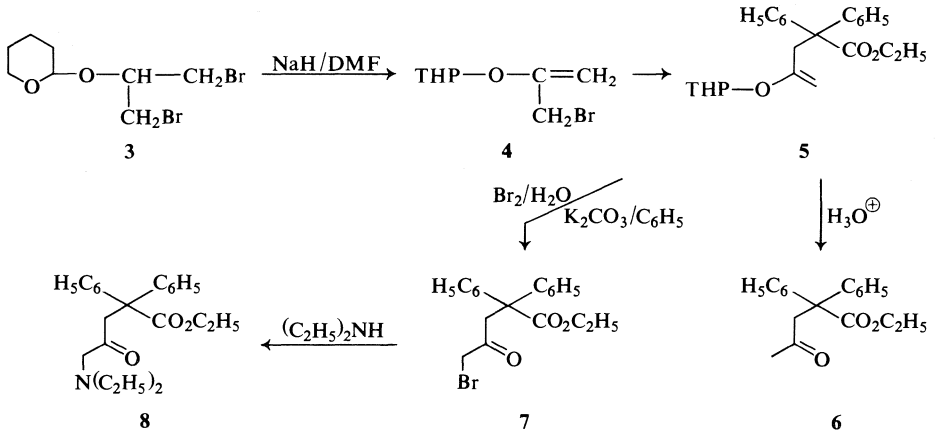


at 0°, but on warming to 10–20° a brisk evolution of hydrogen occurred.[3,4] Addition of ethyl diphenylacetate to the reaction mixture, which was assumed to contain **4** (THP = tetrahydropyran-2-yl), caused a further gas evolution, and after aqueous workup, the enol ether **5** was obtained. Acid catalyzed hydrolysis of **5** gave ethyl-2,2-diphenyllevulinate (**6**). Various reaction conditions for the preparation of **6** were studied (see Table 1, trials *a*, *b*, and *c*), and it was found that a 1.5:1 molar ratio of the dibromide to ethyl diphenylacetate (trial *b*) consistently gave satisfactory yields of **6**. Under similar conditions (see Table 4 in Experimental), fair to good yields of other compounds containing an acetonyl group could be prepared (see Table 3).[5] For example, 2,2-diphenyl-4-oxovaleronitrile was obtained in 73% yield as compared to a 55% overall yield recently reported (5) for the 2-step propargyl group process (vide supra). In addition, alkylation of the pyrrolidine enamine of cyclohexanone and subsequent hydrolysis gave 2-acetonyl cyclohexanone in 24% yield. This was somewhat lower (40%) than was obtained from the direct alkylation of this enamine with acetonyl bromide (10), but the latter procedure invariably gave a product which was contaminated with ca. 15 mole % of 2 - methyl - 4,5,6,7 - tetrahydrobenzofuran (see Experimental).

Under carefully controlled conditions, it was possible to utilize the intermediate enol ethers for the preparation of compounds containing an ω-substituted acetonyl moiety. For example, the synthesis of the basic keto ester **8** (eq. [2]) was accomplished by the bromination of the tetrahydropyranyl enol ether **5**, under conditions which probably generated hypobromous acid, followed by treatment of the α-bromoketone **7** thus produced with diethylamine. Compound **8** was prepared in 49% overall yield from ethyl diphenylacetate, which is remarkably high when the complex nature of the functionality present in **8** is considered.[5]

Although 3 - bromo - 2 - (tetrahydropyran - 2-yloxy)propene (**4**) served notably well as a masked acetonyl group, several instances were envisioned where a 3-bromo-2-alkoxy propene (**9**) would be

[3]The elimination of the elements of hydrogen bromide from β-halogeno ethers with powdered potassium hydroxide is well known (9).

[4]Aqueous workup of the reaction at this stage gave a benzene soluble oily mixture which readily decolorized bromine in carbon tetrachloride, rapidly gave a precipitate of silver bromide with aqueous alcoholic silver nitrate, and which had a medium intensity i.r. absorption at 1634 cm^{-1}. This mixture was judged to contain 60–70% of compound **4** (THP = tetrahydropyran-2-yl) by comparison of the intensity of the n.m.r. signal for the allylic methylene group (singlet at δ 3.88) or the C-2 proton of the tetrahydropyranyl moiety (singlet with fine structure at δ 4.78) with that (singlet with fine structure at δ 1.68) ascribed to the protons on C_3–C_5 of the tetrahydropyran ring. The resonance(s) for the olefinic protons were obscured by the absorptions due to the contaminant(s).

[5]A referee has commented that the main advantage of the 2-alkoxyallyl bromides described herein over bromoacetone, lies in the facile preparation of substituted acetonyl compounds such as **8** from the former. The powerful lachrymatory properties of bromoacetone as well as its poor bench stability (bromoacetone stored at 0° in brown bottles becomes dark colored after 2–3 months and must be redistilled before use; cf., **3** in Experimental) makes **3** (hence **4**) attractive as a source of the acetonyl group. The generality of this approach to acetonyl substituted compounds would, however, be greatly increased if a simple ex situ synthesis of pure 3-bromo-2-methoxypropene, or a derivative thereof, could be devised.

TABLE 1

Determination of the optimum conditions for the preparation of **6**

Trial	Alkylating agent: Compound	Mode of addition*	mmoles†	Reaction time (h)	Yield‡ of **6** (%)	Number of runs
a	**3**	N	10	17	31–57	4
b	**3**§	I	15	13–15	66–69	2
c	**4**‖	N	12¶	22	44	1
d	**11****	I	15	16	73	1
e	**9***a*††	N	10–15‡‡	17	50–59	2
f	**9***b*	N	15‡‡	18	59	1

*N = Normal, i.e. alkylating agent added to sodium salt of ester and excess sodium hydride. I = Inverse; ester added to alkylating agent and sodium hydride.
†Ten mmoles of the ester were used throughout.
‡Yield of pure product.
§Assumed to involve the in situ generation of **4**.
‖Generated ex situ; see footnote 4 in text.
¶Based on the assumption that the mixture described in footnote 4 in text was pure **4**.
Assumed to involve the in situ generation of **9*a*.
††Prepared according to (2).
‡‡These quantities were adjusted for the presence of the isomeric 1-bromo-2-alkoxypropene.

synthetically more versatile.[6] We were surprised to discover that one such compound, 3-bromo-2-methoxypropene (**9***a*), was reported (2) to be the sole thermolysis product of bromoacetone dimethyl ketal. Repetition of this reaction gave a

[3] $CH_3-C(OR)_2-CH_2Br \longrightarrow$

R = CH_3, C_2H_5

$CH_2=C(OR)-CH_2Br$ + $CH_3-C(OR)=CHBr$

9 **10**

a R = CH_3 *a* R = CH_3

b R = C_2H_5 *b* R = C_2H_5

product in about 40% yield, which was shown by nuclear magnetic resonance (n.m.r.) spectroscopy to contain only 43% of the desired alkoxyallyl bromide **9***a* admixed with 50% of 1-bromo-2-methoxypropene (**10***a*) and 7% bromoacetone (eq. [3]). A similar reaction with the diethyl ketal gave a mixture which was significantly richer in the required component **9***b* (75–77% **9***b*, 19–25% **10***b*, and 0–4% bromoacetone). It is probable that the thermolysis products of the other bromoacetone dialkyl ketals studied by Bruce and Ban (2) were also mixtures. The mixtures containing **9***a* and **9***b* were tested as sources of the acetonyl group,[7] however, as judged from the yields of **6** (see Table 1, trials *e* and *f*), they did not have any significant advantages over **4**. Consequently, a method, analogous to that which had been used for the synthesis of **4** from **3**, was then applied to the in situ generation of **9***a* free of **10***a*. Dehydrohalogenation of 2-methoxy-1,3-dibromopropane [prepared by the aluminum chloride catalyzed diazomethane methylation (12) of 1,3-dibromo-2-propanol][8] was effected by briefly heating a DMF solution of this compound with sodium hydride at 60° (eq. [4]). The resulting solution, which presumably contained **9***a*, also was a useful source of the acetonyl group. For example, ethyl-2,2-diphenyllevulinate (**6**) and 2-acetonyl cyclohexanone were prepared therefrom in 73 (see trial *d*, Table 1) and 19% yields, respectively. The utilization of **9***a* for the synthesis of compounds containing a 3-substituted acetonyl moiety has not yet been examined.

[6]For example, reaction of the tetrahydropyranyl enol ether **5** with an aryl diazonium salt would be expected to produce a mixture of 2 hydrazones, *a* and *b*, whereas the corresponding alkoxy compound would give only *a* (11).

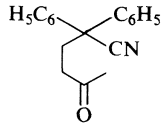
5 $\xrightarrow{ArNHNH_2}$ H_5C_6, C_6H_5, $CO_2C_2H_5$, O, NHHAr (*a*) + HO, O, H, NNHAr (*b*)

[7]Bruce and Ban (2) utilized these mixtures to prepare a series of 5-substituted-5-(2-alkoxyallyl)barbituric acids, and also to alkylate diethyl allylmalonate, but curiously, none of these compounds were converted to their acetonyl derivatives.

[8]This compound is not readily prepared directly from allyl bromide (see (13)).

[4] $BrCH_2\underset{OH}{\underset{|}{C}}HCH_2Br + CH_2N_2 \xrightarrow{AlCl_3} BrCH_2\underset{OCH_3}{\underset{|}{C}}H-CHBr \xrightarrow[60^\circ]{NaH/DMF} CH_2=\underset{OCH_3}{\underset{|}{C}}CH_2Br$

11 **9a**

[5] $THP-O-\underset{CH_2Br}{\underset{|}{CH}}-CH_2CH_2Br \longrightarrow THP-O-\underset{CH_2}{\underset{||}{C}}-CH_2CH_2Br \longrightarrow \longrightarrow$ 

12 **13**

Finally, it was of interest to determine the feasibility of extending the principles discussed above to the introduction of groups other than the acetonyl moiety. Therefore, the tetrahydropyranyl ether **12** was subjected to the elimination conditions described above. Addition of diphenylacetonitrile to this solution gave, after the usual workup, the δ-ketonitrile **13** in 36% yield (eq. [5]) (isolated as the crystalline semicarbazone; see Table 3). A somewhat purer product was obtained (37%) when the dibromide **11** was added to the sodium salt of diphenylacetonitrile and an excess of sodium hydride (as in trial *a*, Table 1).

A number of other synthetic applications of the principles described herein will be submitted for publication in the near future.

Experimental

The melting points were determined in a Gallenkamp melting point apparatus and are not corrected. The infrared (i.r.) spectra were recorded with a Perkin–Elmer 237-B grating spectrophotometer and a Unicam SP-200G i.r. spectrophotometer. The n.m.r. spectra were recorded at 60 Mc.p.s. on a Varian A-60A spectrometer and are expressed in p.p.m. (δ) from internal tetramethylsilane.

1,3-Dibromo-2-(tetrahydropyran-2-yloxy)propane (3)

1,3-Dibromo-2-propanol (217.9 g, 1 mole) containing 12 drops of 48% hydrobromic acid was cooled to 0° with stirring, and 132 g (1.5 moles) of dihydropyran were added dropwise at a rate such that the reaction temperature did not exceed 10°. After 1 h at 0° and 17 h at room temperature, 100 ml of dichloromethane and 10 g of potassium carbonate were added, and the mixture was stirred for 1/2 h. The solids were removed by filtration, the filtrate was concentrated *in vacuo*, and the residual oil was fractionally distilled under high vacuum from 40 g of potassium carbonate. A forerun, b.p. 68–83°/0.06–0.10 mm, was discarded, and the fraction with b.p. 76–83°/0.002–0.005 mm (232.7 g, 77.1%) was collected. A portion of the product was redistilled, and a center cut, b.p. 76°/0.002 mm, was analyzed.

Anal. Calcd. for $C_8H_{14}Br_2O_2$: Br, 52.93. Found: Br, 53.20.

1,3-Dibromo-2-(tetrahydropyran-2-yloxy)propane can be stored at 0° for at least 6 months with no observable loss in its ability to serve as a source of the acetonyl group.

The n.m.r. and i.r. spectra of this and the other halogeno compounds prepared in this work are collected in Table 2.

1,4-Dibromo-2-(tetrahydropyran-2-yloxy)butane (12)

This tetrahydropyranyl ether was prepared in 43% yield from 1,4-dibromo-2-butanol (15) in the manner described above. It had b.p. 92–93°/0.002 mm and was used without further characterization.

1,3-Dibromo-2-methoxypropane (11)

Commercial 1,3-dibromo-2-propanol was strongly acidic to litmus paper, and consequently, a dichloromethane solution of the alcohol was stirred with a paste of sodium carbonate and water until neutrality was achieved. After removal of the solvent, the alcohol was distilled *in vacuo*, and the fraction, b.p. 83–85°/12 mm was collected.

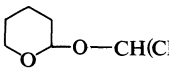
A solution of 1,3-dibromo-2-propanol (23.5 g, 107 mmoles) in 150 ml of dry ether containing 800 mg of anhydrous aluminum chloride, was cooled to 0° with stirring. An ethereal solution of diazomethane (prepared from 41.2 g of nitrosomethylurea) was added dropwise over a 1 h period, then stirring at 0° was continued until gas evolution had become slow (4.5 h). A few drops of acetic acid were added and the mixture was filtered through Celite. The filtrate was washed successively with 10% hydrochloric acid and water, dried over sodium sulfate, and evaporated *in vacuo*. The residual oil, which contained some starting material, was taken up in dichloroethane and this solution was placed on a dry packed column of 400 g of Fluka neutral alumina (activity II). The product was eluted with dichloroethane and was contained in the first 150 ml of the eluate. The solvent was evaporated and the residue was distilled *in vacuo* to give 17.89 g (73%) of a colorless oil, b.p. 72–73°/11 mm [lit. (12), b.p. 83°/13 mm].

3-Bromo-2-methoxypropene (9a) and 1-Bromo-2-methoxypropene (10a)

Bromoacetone dimethyl ketal was thermally cracked by fractionation in a Nester–Faust spinning band column, according to the method described by Bruce and Ban (2). A fraction, b.p. 60.5–61.5°/70 mm [lit. (2), b.p. 65–67°/60–62 mm] was obtained in 41% yield. It was shown by n.m.r. spectroscopy to consist of a mixture of 50% 1-bromo-2-methoxypropene, 43% 3-bromo-2-methoxypropene, and 7% bromoacetone.

TABLE 2

Spectral properties of some bromo compounds

Compound (No.)		Infrared (cm^{-1})*	Nuclear magnetic resonance (δ)†,‡
	(3)	1131, 1034, 981	1.65(bs,6H), 3.28–4.47(m,7H), 4.67 (bs,1H)§
$CH_3O—CH(CH_2Br)_2$	(11)	1101,1081	3.50(s,3H), 3.58(s,4H), 3.85(quin.,1H)
$CH_3O—C(=CH_2)—CH_2Br$	(9*a*)	1663(m),1634, 1308,1212,1169, 1138,1066,862,824	3.65(s,3H), 3.92(s,2H), 4.15(d,1H; J_{AB} = 2.6), 4.35(d,1H; J_{AB} = 2.6)
$CH_3O—C(=CHBr)—CH_3$	(10*a*)		2.00(s,3H), 3.58(s,3H), 5.20(s,1H)
$CH_3CH_2O—C(=CH_2)—CH_2Br$	(9*b*)	1664(m),1631,1306 1206,1190,1139 1070,854(m),816	1.35(t,3H; J = 7.2), 3.87(q,2H; J = 7.2), 3.92(s,2H), 4.16(d,1H; J_{AB} = 2.5), 4.35(d,1H; J_{AB} = 2.5)
$CH_3CH_2OC(=CHBr)—CH_3$	(10*b*)		1.20(t,3H; J = 7.0), 2.02(s,3H), 3.57(q,2H; J = 7.0), 5.23(s,1H)

*Infrared spectra measured as neat liquids.
†Recorded in deuteriochloroform with internal tetramethylsilane unless specified otherwise. J values given in c.p.s.
‡bs = Broad singlet, d = doublet, m = multiplet, q = quartet, quin. = quintet, s = singlet, and t = triplet.
§Measured in carbon tetrachloride.

3-Bromo-2-ethoxypropene (9b) and 1-Bromo-2-ethoxypropene (10b)

Bromoacetone diethyl ketal was thermally cracked as above to give an oil, b.p. 53–55°/26 mm, in about 50% yield. This fraction was shown by n.m.r. spectroscopy to be a mixture of 75–77% 3-bromo-2-ethoxypropene, 19–25% 1-bromo-2-ethoxypropene, and 0–4% bromoacetone. This mixture was not further characterized.

Conditions for the Alkylation Reaction

The preparation of ethyl-2,2-diphenyllevulinate (**6**) exemplifies a typical procedure; modifications are described below as well as in Tables 1 and 4.

A 100 ml, 3-necked flask was flame dried and then charged with 1200 mg (27.5 mmoles) of a 55% dispersion of sodium hydride in mineral oil, while a flow of purified dry nitrogen was maintained through the apparatus. The sodium hydride was freed of the carrier by washing with several portions of hexane, and then it was layered with 30 ml of dry DMF and cooled with stirring to 0°. A solution of 4.53 g (15 mmoles) of 1,3-dibromo-2-(tetrahydropyran-2-yloxy)propane in 5 ml of dry DMF was added all at once, and the apparatus was removed from the cooling bath. At 10° hydrogen evolution commenced and thereafter the reaction temperature rose steadily, but was not allowed to exceed 25°. When the evolution of gas had become slow (ca. 45 min), the mixture was cooled to 0°, and 2.40 g (10 mmoles) of crystalline ethyl diphenylacetate were added all at once. The cooling bath was removed, and the reaction temperature was maintained at 20–25° until gas evolution had become slow. The reaction mixture was stirred at room temperature for 13–15 h under a slight positive pressure of nitrogen. The solution was then poured into a large volume of cold water containing a little sodium chloride, and the product was extracted into benzene. The extract was washed well with water, dried over sodium sulfate, and the solvent was removed *in vacuo* at 40° leaving a quantitative yield of the crystalline tetrahydropyranyl ether **5**. It had i.r. (neat) absorptions at 1733 and 1636 cm^{-1}. Since it was not readily recrystallized and because it partially decomposed (to **6** and presumably dihydropyran) on sublimation at 80°/0.001 mm, it was used without further purification. The crude enol ether was dissolved in 90 ml of methanol and 10 ml of 10% hydrochloric acid, and the solution was heated at reflux temperature for ca. 10 min. The resultant was concentrated to a volume of about 10 ml *in vacuo*, the mixture was diluted with a large amount of water and the product was extracted into benzene. The extract was washed well with water, dried over sodium sulfate, and then evaporated *in vacuo*. The residue was crystallized from methanol to give 1.752 g of a crystalline solid, m.p. 110–112°. Workup of the mother liquor in the usual manner gave an additional 0.187 g of the product m.p. 109–111°. The spectral data for this compound are given in Table 3.

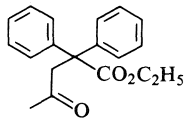
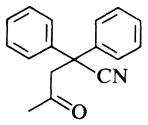
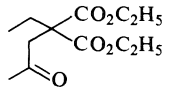
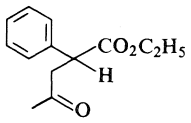
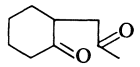
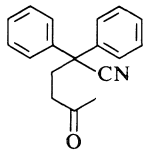
Modifications

(*i*) The rate of dehydrohalogenation of 1,3-dibromo-2-methoxypropane was slower than that of the tetrahydropyranyl ether **3**. As a consequence, the DMF solution containing **11** and excess sodium hydride was thrice heated to 60° and then allowed to cool spontaneously to room temperature. The solution of **9***a* thus obtained was then used as above.

(*ii*) The alkylation of the pyrrolidine enamine of cyclohexanone was carried out under the usual conditions except that a 1:1 molar ratio of the alkylating

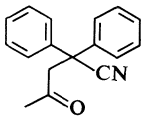
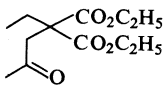
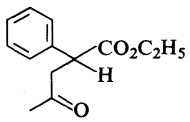
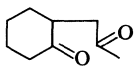
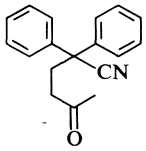
TABLE 3

Yields and properties of some ketonic compounds

Compound	Yield (%)*	Calcd. C	Calcd. H	Found C	Found H	Melting point (°C) or boiling point (°C/mm)	Other means of characterization	
	66–69	77.00	6.80	76.93	6.75	110–112†	n.m.r. (δ)‡	1.13(t,3H;J = 7.0),2.00(s,3H) 3.58(s,2H),4.13(q,2H;J = 7.0) 7.20(s,10H)
							i.r.(cm^{-1})§	1731
	73	81.90	6.06	81.62	6.02	103–105‖	n.m.r.	2.10(s,3H),3.52(s,2H),7.28 (s,10H)
							i.r.	2247(w),1729
							lit. (5)	m.p. 105–107°
	55	59.00	8.25	58.73	8.44	145–150/9¶	n.m.r.	0.87(t,3H;J = 7.5),1.25(t,3H; J = 7.2),2.10(q,2H;J = 7.5), 2.18(s,3H),3.02(s,2H),4.27 (q,2H;J = 7.2)
							i.r.	1757(sh), 1731[neat]
	42	—	—	—	—	95–100/0.04	i.r.	1734,1725[neat]
						36.5–39**	lit. (14)	m.p.41–42. Saponification of the ester gave an acid m.p. 126–127°, [lit.(14)m.p.127°]††
	24	—	—	—	—	95/1.0¶	Identical to an authentic specimen prepared according to ref. 10.	
	36–37‡‡	71.22	6.29	71.35	6.33	171–173	n.m.r.	1.83(s,3H),2.53(m,4H),5.98 (s,2H),7.42(m,10H),8.80(s,1H)
							i.r.	3520,3468,3400,3378,3208 1697,1569

*Yields of pure products.
†After crystallization from methanol and sublimation at 85°/0.001 mm.
‡See † and ‡ in Table 2.
§Measured in chloroform unless specified otherwise.
‖After crystallization from 2-propanol and sublimation at 90°/0.001 mm.
¶Evaporative distillation; air bath temperature.
**After crystallization from petroleum ether b.p. 60–90°.
††After crystallization from ether.
‡‡Yield, analysis, m.p., and spectral data are those of the semicarbazone.

TABLE 4
Conditions for the preparation of some ketonic compounds

Compound	Moles dibromide*/mole active methylene compound	Reaction temperature (°C)	Time (h)
	1.5	25	2
	1.5	25	19
	1	50	17
	1	25	15
	1.5	25	15

*Dibromide **3** was used for the first 4 compounds and dibromide **12** for the last compound.

agent to the enamine was used (see Table 4). When the reaction was completed the solution was poured into a large excess of water and then left at room temperature for 1 h. The product was then isolated in the usual way by extraction with benzene. Removal of the solvent gave the crude keto enol ether (4.90 g from a 20 mmole reaction using **4** prepared in situ) which was taken up in 200 ml of dichloromethane. The solution was stirred vigorously at room temperature with 35 ml of 10% hydrochloric acid and 185 ml of water. After 1 h, the organic phase was separated, washed well with water, and dried over sodium sulfate. The solvent was removed *in vacuo* leaving an oil which was distilled *in vacuo*. The material thus obtained, b.p. 70–110°/0.7 mm (2.72 g) was shown to be a 2 component mixture by thin-layer chromatography (t.l.c.) on alumina (benzene). This mixture was taken up in benzene and placed on a column of 100 g of Fluka neutral alumina (activity II; packed in benzene). The chromatogram was developed with benzene (250 ml) and then chloroform (350 ml). The impurity was contained in the benzene eluate, the product in the chloroform eluate. After removal of the solvent *in vacuo*, the residual oil was evaporatively distilled at 95°/1 mm [lit. (10), b.p. 91–93°/1.1 mm], to give 745 mg of a colorless liquid (see Table 3) with an i.r. (neat) absorption at 1713 cm^{-1}. When prepared by the method of Baumgarten *et al.* (10), 2-acetonylcyclohexanone was contaminated with ca. 15 mole % of 2-methyl-5,6,7,8-tetrahydrobenzofuran (determined by integration of the absorption for the olefinic proton at δ 5.82). The i.r. spectrum of 2-acetonylcyclohexanone obtained in this way had a weak band at 1627 cm^{-1}, but was otherwise identical to the specimens prepared by our procedures.

(*iii*) For the preparation of 2,2-diphenyl-5-oxocapronitrile (**13**), the best procedure was to add the dibromide **12** to the sodium salt of diphenylacetonitrile and excess sodium hydride. When the reaction was completed, the crude product was taken up in methanol and treated with an excess of aqueous–methanolic semicarbazine. The product, m.p. 168–171°, crystallized from solution and was collected by filtration. After two crystallizations from aqueous alcohol (3:4) the melting point was raised to 171–173° (see Table 3).

*Ethyl-2,2-diphenyl-5-diethylaminolevulinate (**8**)*

To a vigorously stirred cooled (5°) mixture of potassium carbonate (415 mg, 3 mmoles) and 55 μl of water (55 mg, 3.05 mmoles) in 25 ml of benzene containing 1.14 g (3 mmoles) of the tetrahydropyranyl ether **5**, was added a solution of 528 mg (0.17 ml, 3.3 mmoles) of bromine in 5 ml of benzene at a rate such that the reaction temperature did not exceed 10°. When the addition was completed,

the cooling bath was removed, and the mixture was stirred vigorously for 20 min. At the end of this time, the mixture was again cooled to 5°, and 438 mg (0.63 ml, 6 mmoles) of diethylamine were added all at once. The cooling bath was removed, and after stirring for 2 h at room temperature, a few mls of sodium carbonate solution (200 g/l) and 50 ml of water were added. The organic phase was separated and combined with a benzene extract of the aqueous phase. The benzene phase was extracted alternately with 10% hydrochloric acid (4 × 30 ml) and water (4 × 30 ml). The aqueous acidic extract was made basic with sodium carbonate solution (200 g/l), and the liberated base was extracted into dichloromethane. The extract was dried over sodium sulfate, and the solvent was removed *in vacuo* leaving 0.64 g of a yellow oil which was converted to its hydrobromide salt in ether. The crude salt was taken up in about 50 ml of hot 2-propanol, and this solution was made up to ca. 250 ml with ether. A beautifully crystalline solid, m.p. 195–197° was obtained in 48.6% yield (0.653 g). The n.m.r. spectrum (free base in $CDCl_3$) had resonances at δ 0.93 (t, 6H; J = 7.1), 1.17 (t, 3H; J = 7.1), 2.48 (q, 4H; J = 7.1), 3.00 (s, 2H); 3.73(s, 2H), 4.18(q, 2H; J = 7.1), and 7.23 (m, 10H). The i.r. spectrum (Nujol mull) of the salt had a strong absorption at 1734 cm^{-1}.

For analysis, the above material was thrice crystallized from 2-propanol. The melting point was thus raised to 198–200°.

Anal. Calcd. for $C_{23}H_{29}NO_3 \cdot HBr$: C, 61.60; H, 6.74; N, 3.12. Found: C, 61.71; H, 6.69; N, 3.39.

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