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REVIEW

Synthetic Routes to 2-Hydroxy-3-methylcyclopent-2-en-1-one and Related Cyclopentane-1,2-diones: A Review

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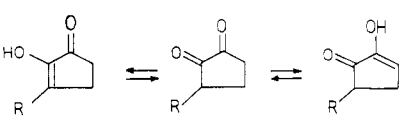
Synthetic routes to 2-hydroxy-3-methylcyclopent-2-en-1-one are reviewed. This compound is produced during the thermal and base-catalyzed degradation of certain carbohydrates and is a product of the destructive distillation of wood. As a component of the roasted coffee aroma complex and of maple syrup flavor extract, it has important organoleptic properties.

A crystalline compound, subsequently identified as 3-methylcyclopentane-1,2-dione, was first isolated 70 years ago from pyroligneous acid, obtained by the dry distillation of beechwood (Meyerfeld, 1912; Rojahn and Rühl, 1926). Many reports of the isolation of this substance among the products of pyrolytic degradation of wood and carbohydrates have ensued [see references in Erickson and Collins (1965), Sato et al. (1967), and Fiddler et al. (1970)]. The compound was also produced when ground spruce wood, previously extracted with acetone, was digested with sodium hydroxide solution (Enkvist et al., 1954).

In 1963, 3-methylcyclopentane-1,2-dione was identified, along with some other cyclic 1,2-diketones, as a component of the roasted coffee aroma complex (Gianturco et al., 1963), and shortly afterward, it was found in maple syrup flavor extract (Filipic et al., 1965). The latter authors point out that during the conversion of maple sap to syrup by boiling, "the solution passes through an alkaline phase ... being at a maximum pH of about 9 for some time ...". Such conditions are clearly conducive to the formation of this cyclopentane-1,2-dione from certain carbohydrates [cf. Enkvist et al. (1954), Fray (1961), and Shaw et al. (1968)] (vide infra).

Meyerfeld (1912) in the original publication drew attention to the characteristic organoleptic properties of the compound: "Er besitzt einen eigentümlichen, angenehmen Geruch und einen süssen, etwas brennenden Geschmack, der sowohl an Lakritzen wie an frische Walnüsse erinnert". These caramel or maplelike qualities have made it an important commerical flavoring agent, designated variously as cyclotene, corylone, ketonarome, nussol, etc. (Cookson and Smith, 1979).

One of the carbonyl groups in the dione is fully enolized (Schwarzenbach and Wittwer, 1947) and early authors favored the structure 1 (R = CH_3) for the enol. Subsequently, arguments were advanced in support of the tautomeric form 2, but later, nuclear magnetic resonance studies provided unequivocal evidence supporting structure 1 (R = CH_3), 2-hydroxy-3-methylcyclopent-2-en-1-one



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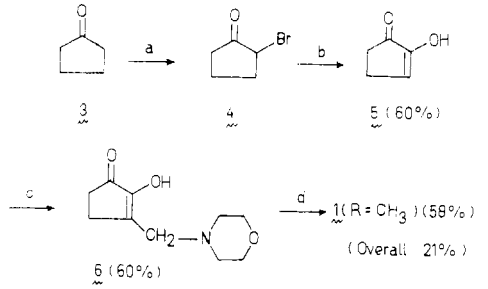
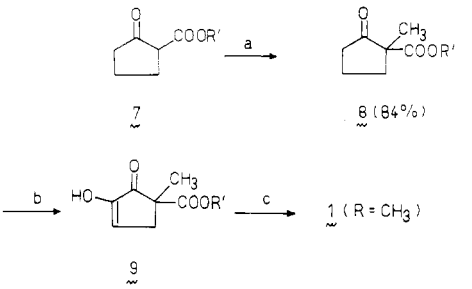
Scheme I[a]



[a] (a) Dioxane dibromide; (b) $FeCl_3$; (c) morpholine, HCHO, dioxane; (d) Zn, HOAc.

Scheme II[a]



[a] (a) NaH, CH_3I, THF; (b) various oxidation procedures (see the text); (c) H_2O, H^+ or OH^- (see the text).

[Bredenberg, 1959, 1960; for other relevant references see Erickson and Collins (1965)].

Studies of structure–activity relationships with respect both to sweet taste (Shallenberger and Acree, 1969) and to odor (Ohloff and Giersch (1980) suggest that for both sensations, interaction between an active compound and the appropriate receptor requires, inter alia, the presence in the molecule of a proton donor and a proton acceptor, correctly located not more than 3 Å apart. Although intramolecular hydrogen bonding seems to be permissible to a degree, if it is too strong, the ability to elicit sweet taste is restricted (Shallenberger and Acree, 1969).

With its caramel odor, 1 (R = CH_3) appears to meet the criteria for this model, and Ohloff and Giersch (1980) do, in fact, comment on the related aroma of some other cyclic 1,2-diketones.

In large part because of the importance conferred on it by its organoleptic properties, 1 (R = CH_3) has been the target of much synthetic activity. Indeed, its value does not reside solely in its aroma and flavor: the compound has also been found useful as a synthetic precursor of cyclopentenoid natural products, including dihydrojasmone (Erickson and Collins, 1965; Dahill, 1966) and methylenomycin B (Jernow et al., 1979). The object of this review is to bring together most, if not all, of the synthetic routes to 1 (R = CH_3) reported in the literature, grouping them where possible under headings which identify the most important common features of the various strategies employed. It is hoped that this will be useful for evaluation of synthetic approaches to the title compound and of some interest in the context of organic synthesis in general.

SYNTHETIC ROUTES

From Cyclopentanone. A facile analysis of the structural features of 1 (R = CH_3) and its homologues identifies these compounds as simple derivatives of cyclopentanone and suggests that they should be accessible from the latter by introduction of carbonyl and methyl (alkyl) functionality using appropriate methodology. A synthesis of 1 (R = CH_3) has indeed been accomplished from cyclopentanone by the sequential introduction of these groups (Sato et al., 1973) (Scheme I), though the overall yield was modest (~20%).

It may be noted that the methyl group cannot be introduced at C-3 of 5 by using "normal" alkylation conditions, because of the propensity of the enolized α-diketone system to undergo O-alkylation. A rationale for this behavior in terms of the calculated charge distribution of the monoanion has been provided by Kende and Eilerman (1973). These authors have accomplished the desired objective (in 60% yield from 5) by alkylation with excess methyl iodide of the *dianion*, prepared in tetrahydrofuran at −78 °C by treatment with 2 equivalents of lithium diisopropylamide. Under these conditions no O-alkylation or dialkylation was observed.

In Sato's 1973 synthesis, the alkylation problem was circumvented by means of a Mannich reaction and subsequent zinc reduction (Scheme I).

From 2-Carbalkoxycyclopentanone. In an earlier approach, Scheme II, Sato et al. (1967) introduced the substituent groups in the reverse sequence, using the readily available 2-carbethoxycyclopentanone 7 (R′ = C_2H_5) as the starting material. The sodium enolate of the latter was smoothly alkylated with methyl iodide to give 8 in 84% yield. A variety of procedures was investigated for oxidation of 8 (R′ = C_2H_5) to the α-diketone 9 (R′ = C_2H_5) (Sato et al., 1967, 1970). Thus, selenium dioxide oxidation of the former afforded the latter in 44% yield, and hydrolysis/decarboxylation with aqueous sulfuric acid gave 1 (R = CH_3) (51%). Reaction of 8 (R′ = C_2H_5) with *n*-butyl nitrite in the presence of dry hydrogen chloride, followed by acid hydrolysis without isolation of the intermediate, provided a somewhat better (35%) overall yield of 1 (R = CH_3).

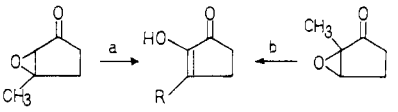
Alternatively, 8 (R′ = C_2H_5) could be monobrominated in the 5-position, and the bromide oxidized with dimethyl sulfoxide in the presence of epichlorohydrin, to afford a 59% yield of 9 (R′ = C_2H_5), which on base-catalyzed hydrolysis and decarboxylation furnished 1 (R = CH_3) (63%; 29% overall from dimethyl adipate). The function of the epichlorohydrin is to act as a scavenger for HBr generated during the interaction of the bromo ketone with dimethyl sulfoxide. In the absence of the epoxide, the HBr is oxidized by dimethyl sulfoxide to bromine, and bromination of the newly formed cyclopentane dione occurs.

The most effective and economical oxidation of 8 is achieved by halogenation. Thus, bromination of 8 (R′ = C_2H_5) in CCl_4 at room temperature gave the 5,5-dibromo derivative (85%). Treatment of the latter with morpholine, followed by alkaline hydrolysis, afforded 1 in 49% yield (overall 30%) (Sato et al., 1970). Leir (1970) developed a closely similar synthesis using the corresponding methyl esters and employing chlorine rather than bromine as the oxidizing agent. This and other experimental modifications led to substantially improved overall yields of 1 (R = CH_3) [57%, or 63% if intermediates were not purified en route (!)]. A parallel sequence in which ethyl iodide was used as the alkylating agent gave the unstable ethyl homologue 1 (R = C_2H_5), also a flavor component of roasted coffee, in overall yield of 70%.

It is interesting to note than in one of the earliest synthesis of 1 (R = CH_3) reported, oxidation of 2-methylcyclopentanone, was similarly accomplished by chlorination followed by hydrolysis in boiling water (Gault and Burkhard, 1937).

Syntheses via 2,3-Epoxycyclopentanones. House and Wasson (1957) studied the rearrangement of cyclic 2,3-epoxy ketones under catalysis by Lewis acids. They observed that, while 2,3-epoxycyclohexanones gave α-

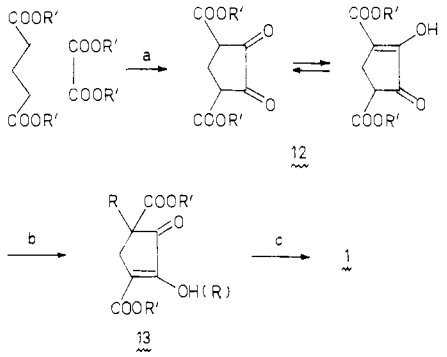
Scheme III[a]



10 1 (R = CH_3) 11

[a] (a) BF_3-Et_2O or H^+; (b) 2% H_2SO_4 in CH_3COOH.

Scheme IV[a]



[a] (a) sodium alkoxide, Et_2O; (b) sodium alkoxide, RI, EtOH or DMF; (c) H_2O, H^+.

formyl- (or α-acyl-) cyclopentanones often accompanied by 1,2-cyclohexanediones on treatment with boron trifluoride etherate, only 1,2-cyclopentanediones were produced from 2,3-epoxycyclopentanones.

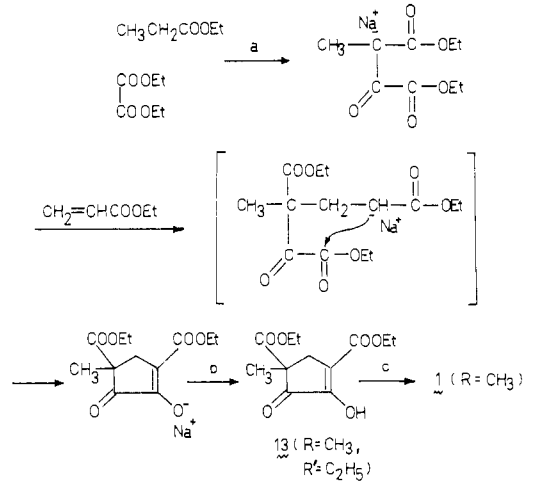
House and Wasson obtained 1 (R = CH_3) in 80% yield by treatment of **10** with boron trifluoride etherate in benzene solution at room temperature for 2 min (Scheme III). In a patented synthesis by Calame et al. (1973), the rearrangement of **10** to 1 (R = CH_3) is catalyzed by perchloric acid. The starting material for this route is hexane-2,5-dione, which is cyclized in aqueous alkali to 3-methylcyclopent-2-en-1-one (81%). Epoxidation of the latter using alkaline hydrogen peroxide affords **10** (50%). The desired rearrangement to 1 (R = CH_3) is effected in 83% yield (overall 34%) by heating **10** in acetone solution containing perchloric acid. Using aqueous 2% sulfuric acid as the catalyst, a 69% yield of 1 (R = CH_3) was obtained from **10** (Langin-Lanteri and Huet, 1976).

Nazarov and Akhrem (1956) reported that traces of 1 (R = CH_3) were also formed when the isomeric 2,3-epoxy-2-methylcyclopentanone, **11**, was treated with acid. This rearrangement, which appears to involve a 1,2-methyl migration, was further developed by Barco et al. (1975). These authors observed that heating **11** in acetic acid containing 2% concentrated sulfuric acid gave a substantially better yield (58%) of 1 (R = CH_3) than the boron trifluoride catalyzed rearrangement.

Syntheses Employing Oxalate. If oxalate is used in the construction of the ring, cyclopentane-1,2-diones are produced directly, and the necessity of a subsequent oxidation step is obviated. Thus, the patented synthesis by Litchenberger and Litchenberger (1939) involves alkylation of 3,5-dicarbalkoxycyclopentane-1,2-dione, **12**, obtained by condensation of glutaric and oxalic acid esters. Hydrolysis and decarboxylation then afford directly the 3-alkyl-2-hydroxycyclopent-2-en-1-one (Scheme IV). This approach has been used for synthesis of 1 (R = CH_3) by Hesse and Böckmann (1949) and by Gianturco and Friedel (1963), who also prepared the 3-ethyl homologue 1 (R = C_2H_5) in a like manner.

Of interest is the observation by both groups that optimum yields of the C-alkylated products are obtained by using 2 equiv of base and excess alkylating agent. Hesse

Scheme V[a]



[a] (a) NaOEt, xylene or Et_2O; (b) H^+, H_2O; (c) H_2O, H^+, Δ.

and Böckmann (1949) discuss the unusual properties of the anionic species involved. Parenthetically, it may be noted that significant O-alkylation can accompany C-alkylation of **12** under some conditions (Gianturco and Friedel, 1963; Barco et al., 1974).

The above synthesis (cf. Scheme IV) has been conducted as a one-pot sequence and, with some additional experimental modifications, affords the highest yield of 1 (R = CH_3) reported for any synthesis from simple readily available acyclic precursors (80% from diethyl glutarate) (Strunz and Lal, 1982).

Van Brussel and Vandewalle (1976) synthesized 1 (various R groups) by reduction of 2-substituted-3,5,5-triethoxycyclopent-2-en-1-ones using lithium aluminum hydride in tetrahydrofuran. (For the methyl compound, the yield for this transformation was 65%.) The substrates are prepared from the corresponding 3-substituted-cyclopentane-1,2,4-trione, of which oxalate is a precursor.

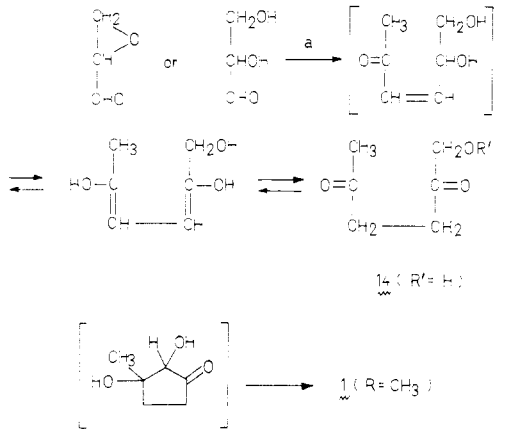
An interesting synthesis, also employing oxalate was published as a patent by Krimen and Norman (1958), and later modified by Tonari et al. (1970) to give enhanced yields. The sequence is illustrated in Scheme V. Although the overall yield was originally quite modest (~15%), the synthesis employs inexpensive readily available chemicals and does not require alkylation with an alkyl halide. It was conducted as far as **13** without isolation of intermediates. The modified experimental conditions developed by Tonari et al. (1970) increased the overall yield to 44%.

Synthesis via Acyclic 1-Hydroxy 2,5-Diketone Derivatives. Reported syntheses involving this kind of intermediate (**14**) differ substantially in the manner of its genesis.

Fray (1961) investigated the formation of 1 (R = CH_3) as a minor product on treatment of glycidaldehyde or glyceraldehyde with acetone and aqueous alkali. He advanced the mechanism depicted in Scheme VI to account for this transformation. The reaction could provide "an explanation for the production of 1 (R = CH_3) from wood by vigorous treatment with alkali, since alkaline degradation of the cellulose and other carbohydrate constituents could give rise to both acetone and glyceraldehyde" (Fray, 1961).

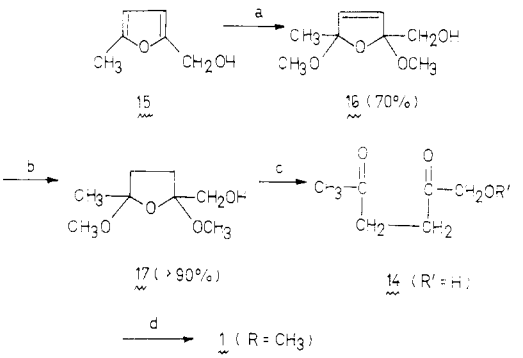
In studying the base-catalyzed degradation of fructose, Shaw et al. (1968) isolated, among other products, the three possible isomeric hydroxybutanones and hydroxyacetone as well as some cyclic 1,2-diones, including 1 (R = CH_3). They demonstrated that most of the cyclic diones could be obtained directly by base-catalyzed interaction of a

Scheme VI[a]



[a] (a) CH_3COCH_3, NaOH, H_2O, Δ.

Scheme VII[a]



[a] (a) CH_3OH, −2e; (b) H_2, Raney Ni; (c) Dowex 50 W; (d) Na_2CO_3, H_2O.

mixture of the above four hydroxy ketones. Thus, hydroxyacetone evidently underwent aldol condensation with its tautomer, 2-hydroxypropanal, to give 14 (R′ = H), which cyclized as above to produce 1 (R = CH_3).

In the synthesis by Shono et al. (1977), Scheme VII, electrochemical oxidation of 5-methylfurfuryl alcohol, 15, in methanol, gave a stereoisomeric mixture of dimethoxy products 16, (70%), which was hydrogenated to 17. Treatment of 17 with an acidic ion exchange resin, followed by aqueous sodium bicarbonate, afforded 1, (R = CH_3) (via 14) in an overall yield greater than 50%.

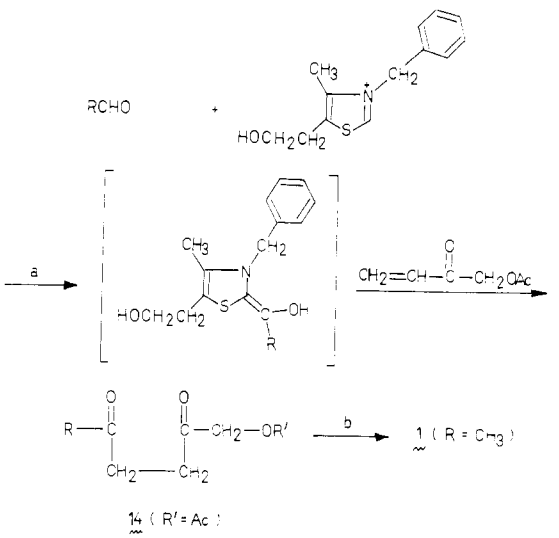
Stetter and Schlenker (1980), Scheme VIII, synthesized 1-acetoxy-2,5-hexane-dione (14, R = Ac) and homologues by conjugate addition to 1-acetoxybut-3-en-2-one of an acyl anion equivalent. The latter was generated from the corresponding aldehyde by base-catalyzed interaction with 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (cf. role of thiamin pyrophosphate in transketolase reaction). Base-catalyzed cyclization of 14 (R = CH_3, R′ = Ac) afforded 1 (R = CH_3) in 47% overall yield.

Syntheses Involving Cyclization of 1,5-Dicarbonyl Compounds to α-Ketols. Thiazolium ion catalysis was also used effectively in a synthesis of 1 by Cookson and Lane (1976), who by this means cyclized glutaraldehydes to the corresponding α-hydroxycyclopentanones (Scheme IX). The overall yield of 1, (R = CH_3) prepared by the route depicted in Scheme IX, was 50%.

In an earlier synthesis, Naoshima et al. (1974) prepared the same acyloin intermediate 17 [via the bis(trimethylsilyl) ether], from diethyl 2-methylglutarate, using conventional acyloin conditions.

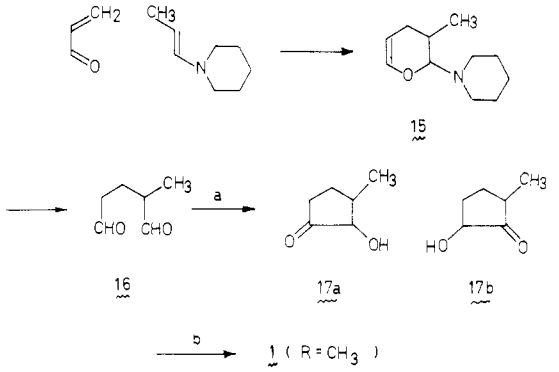
The quest for a short, operationally simple, and efficient synthesis of 1 (R = CH_3) from low cost materials later led

Scheme VIII[a]



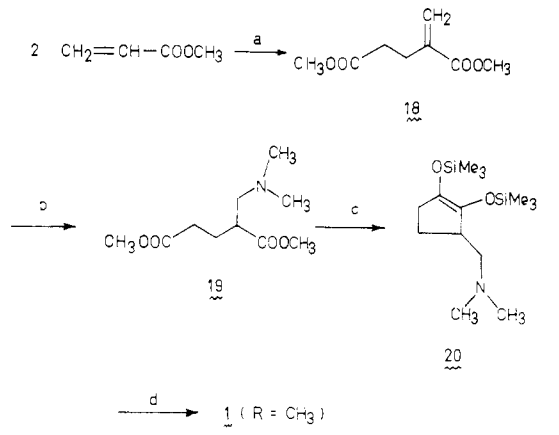
[a] (a) Et_3N, dioxane; (b) $NaOCH_3$, EtOH.

Scheme IX[a]



[a] (a) 3-benzyl-4-methylthiazolium chloride, CH_3CN, Et_3N, 80 °C; (b) $Cu(OAc)_2$, CH_3OH, H_2O, HOAc.

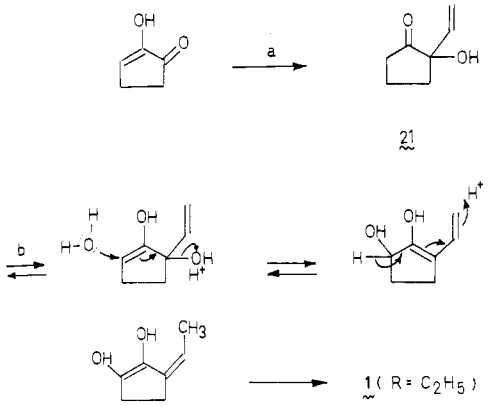
Scheme X[a]



[a] (a) Tris(cyclohexyl)phosphine-CS_2 complex, pyridine, Δ; (b) Me_2NH, CH_3OH; (c) Na, toluene, Me_3SiCl, Δ; (d) silica gel.

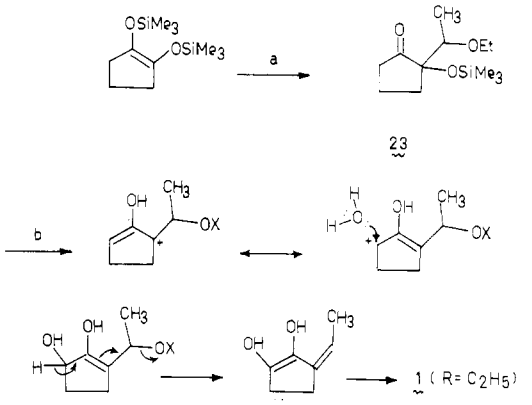
Cookson and Smith (1979) to develop the related alternative synthesis shown in Scheme X. Their original plan was to cyclize the dimer, 18, of methyl acrylate, under acyloin reaction conditions, the anticipated product being recognizable as a protected tautomer of 1 (R = CH_3). The failure of 18 to undergo acyloin cyclization was attributed to the presence of the unsaturation, prompting the authors to protect the double bond as the dimethylamine adduct, 19, prior to the reaction. The resulting acyloin product,

Scheme XI[a]



[a] (a) Vinylmagnesium bromide, THF; (b) 20% H_2SO_4, 60 °C.

Scheme XII[a]



[a] (a) $CH_3CH(OEt)_2$, BF_3-Et_2O; (b) PTSA, benzene.

20 (78%), on elution through a column of silica gel afforded **1** (R = CH_3) (55% overall from acrylate dimer).

A synthesis of **1** (R = C_2H_5) from 1,2-bis[(trimethylsilyl)oxy]cyclopentene, published recently by Pattenden and Teague (1982), might also be considered to belong under the above heading but is instead deferred until the next section, where it is juxtaposed with the study of Maignan and Rouessac (1974) because of the formal similarity of the rearrangements involved.

Miscellaneous Synthetic Routes. Maignan and Rouessac (1974) investigated the acid-catalyzed rearrangement of cyclic 2-hydroxy-2-alkenyl 1-ketones, obtained from the reaction of vinylic Grignard reagents with cyclic 1,2-diones. The reaction of cyclopentane-1,2-dione with vinyl magnesium bromide furnished **21**, which, on warming with 20% sulfuric acid, gave a 52% yield of **1** (R = C_2H_5). The mechanism proposed for the transformation is illustrated in Scheme XI.

The spiro epoxide prepared (46%) from 2-ethylidenecyclopentanone also afforded **1** (R = C_2H_5) (35%) on warming with 20% sulfuric acid, possibly via the same intermediates (Maignan and Rouessac, 1976).

As mentioned above, the recent synthesis by Pattenden and Teague (1982) (Scheme XII) appears to involve rearrangements closely similar to those discussed by Maignan and Rouessac (1974). The intermediate **23** is prepared from **22** by aldol reaction with 1,1-diethoxyethane under catalysis by boron trifluoride etherate at −78 °C. Rearrangement to **1** (R = C_2H_5) is effected (57% overall) by heating **23** in benzene solution with *p*-toluenesulfonic acid.

This review concludes with a reference to a remarkable synthesis, which chronologically seems to have been the first preparation of **1** (R = CH_3) to be reported from materials other than wood. Urion (1934) prepared 3,4-dihydroxyhexa-1,5-diene by pinacol-type reduction of acrolein with a zinc–copper couple. Dehydrogenative cyclization of the product over copper at 280 °C afforded, inter alia, a 20% yield of **1** (R = CH_3), identical with material obtained by Dupont and Urion (1933) from pine tar.

CONCLUSIONS

A substantial number of synthetic routes has been reported leading to 3-alkyl-2-hydroxycyclopent-2-en-1-ones, **1**, with varying degrees of efficiency. The considerable amount of attention focused on synthesis of this relatively simple system reflects the importance of **1** (R = CH_3) as a commercially useful organoleptic agent but also in some cases its convenience as a target vehicle for testing novel synthetic methodology [cf. jasmonoids: Ho (1974)].

Many of the approaches described can be (or have been—whether or not specifically mentioned herein) applied to the synthesis of homologous compounds such as **1** (R = C_2H_5), also identified as a component of the roasted coffee aroma complex (Gianturco et al., 1963). Compounds possessing additional alkyl substitution at C-4 or C-5 are also readily accessible by some of the routes.

Registry No. **1** (R = CH_3), 80-71-7.

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ARTICLES

Fiber-Reactive Insecticides for Wool: Organophosphorus Esters of Nitrogen Heterocycles

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O,O-Diethyl phosphorothionate esters and *O*-ethyl *S*-*n*-propyl phosphorothiolothionate esters of some pyridazine and 1,2,4-triazole compounds containing a 2-bromoacryloyl ester substituent have been synthesized and screened for insecticidal activity against the wool-digesting insects *Tineola bisselliella* and *Anthrenus flavipes*. These compounds were found to be hydrolytically unstable when applied to wool from a boiling acidic dye bath. The extent of this hydrolysis has been determined by the development of a method for estimating organophosphorus esters that are covalently bound to the wool.

Recently it has been demonstrated that the suitability of organophosphorus insecticides for protecting wool against insect damage can be improved if they contain a 2-bromoacryloyl ester substituent (Jones et al., 1982). This group was thought to covalently bond these insecticides to the wool so that the resistance to insect damage obtained was retained when the treated wool was washed, dry-cleaned, or exposed to light. In this earlier study the insecticidal properties of a number of different fiber-reactive organophosphorus compounds were evaluated, and the most active compounds found were *O,O*-diethyl *O*-[6-[[2-[(2-bromoacryloyl)oxy]ethyl]thio]-3-pyridazinyl] phosphorothionate and *O,O*-diethyl *O*-[1-[[(2-bromoacryloyl)oxy]methyl]-1,6-dihydro-6-oxo-3-pyridazinyl] phosphorothionate. Although these compounds displayed some promise as durable insecticides for wool, it was thought (Jones et al., 1982) that a significant degree of hydrolysis of the phosphorus ester group occurred when they were applied to wool from an acidic dyebath. Because the insecticide could not be extracted from the wool, the amount present was not determined but was inferred by the degree of feeding damage that occurred when wool treated at different levels was bioassayed against the larvae of *Tineola bisselliella* and *Anthrenus flavipes*.

In recent patent literature (Hoffman et al., 1974, 1975; Bohner et al., 1974; Riebel et al., 1976; Hofer et al., 1976a,b) it has been claimed that when the *O,O*-diethyl phosphorothionate group in a nitrogen heterocycle insecticide is replaced with a *O*-ethyl *S*-*n*-propyl phosphorothiolothionate group, insecticidal activity against a broad spectrum of insects was increased substantially. These phosphorodithioate esters would also be expected to possess better hydrolytic stability than the corresponding diethyl phosphorothionate esters.

In the present study, *O,O*-diethyl phosphorothionate esters and *O*-ethyl *S*-*n*-propyl phosphorothiolothionate esters of some pyridazines and triazoles that contain a 2-bromoacryloyl substituent have been prepared and applied to wool during dyeing. The rate of hydrolysis during application to wool both in the dye-liquor and on the wool has been measured to assess the suitability of fiber-reactive organophosphorus esters based on nitrogen heterocycles for protecting wool against insect damage.

MATERIALS AND METHODS

Preparation of Phosphorus Esters. The compounds used in this study (Tables I and II) and their intermediates were prepared as described below. Where necessary they were purified by liquid chromatography on a Waters Associates Prep LC System 500 using silica gel as the adsorbent and a mixture of ethyl acetate and hexane as the eluting solvent. The compounds were obtained as oils and were characterized by proton nuclear resonance spectrometry (60 Hz) and by microanalysis. A tabulation of the ^{1}H NMR spectra and microanalysis data is provided as supplementary material (see paragraph at the end of paper regarding supplementary material).

O,O-Diethyl *O*-[1-[[(2-bromoacryloyl)oxy]methyl]-6-oxo-3-pyridazinyl] phosphorothionate (compound **9**) and *O,O*-diethyl *O*-[6-[[2-[(2-bromoacryloyl)oxy]ethyl]thio]-3-pyridazinyl] phosphorothionate (compound **11**) were prepared as described previously (Jones et al., 1982). The

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