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ACETOXYPHENYLKETENE. REACTION WITH BIACETYL

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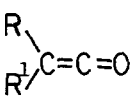
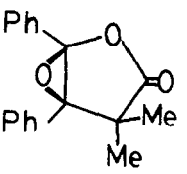
Summary: The generation of acetoxyphenylketene (4) in the cold in the presence of biacetyl yields the single β-lactone 12B, which undergoes a novel rearrangement to the tricyclic orthoester lactone 11 above 130°.

Ketenes have been known since the initial discovery by Staudinger of diphenylketene (1) in 1905[1]. Ketene reactions with carbonyl compounds to give β-lactones are very well known and have been extensively studied[2]. On the other hand, reactions with α-dicarbonyl compounds have been little explored[3]. 1,4-Cycloaddition of diphenylketene to phenanthrenequinone and other o-quinones have been reported[2]. Dimethylketene (2) proved to react in a different way, giving a monolactone derivative of phenanthrenequinone with Lewis acid catalysis[4]. Under similar conditions, (2) reacts with benzil in a different fashion, giving the epoxy-γ-lactone (5). The same authors[4] reported a very complex mixture from the reaction of dimethylketene (2) and biacetyl (10), under acid catalysis.



1, R = R^1 = Ph
2, R = R^1 = Me
3, R = R^1 = H
4, R = OAc, R^1 = Ph



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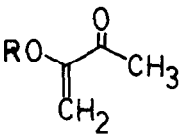
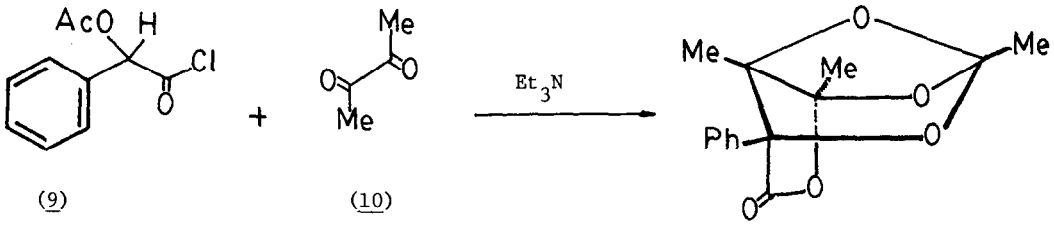


6, R = Ac
7, R = PhCH(OAc)CO
8, R = Ph_2CHCO

Hagemeyer found that ketene (3) reacts with excess biacetyl (10), in the presence of boron trifluoride, to give very poor yields of 3-methyl-3-buten-2-one and 2,3-dimethyl-1,3-butadiene, presumably arising from the decomposition of mono and dilactone intermediates[5]. Spence had previously reported that biacetyl (10) reacts with ketene (3), in the presence of sulphuric acid, affording the enolacetate (6) in low yield[6].

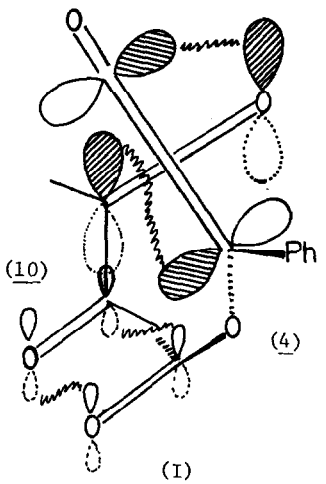
Monoenol derivatives of biacetyl have been used by us as dienophiles in our o-quinodimethane approach to anthracycline antibiotics[7]. In an attempt to prepare the mandelate derivative (7), we obtained the unexpected product (11), as evidenced by chemical and spectroscopic data. Compound (11) was obtained in 45% yield from the reaction of biacetyl (10) with one equivalent of acetoxymandelyl chloride (9) in the presence of one equivalent of triethylamine. Distillation of the oily reaction mixture, after separation of the triethylamine hydrochloride, gave a colorless liquid (bp 132-35°C, 2 mmHg), which solidified (mp 124-25°C) on standing. Its IR spectra showed only one carbonyl absorption at 1800 cm^{-1} (lactone), proving that three of the four

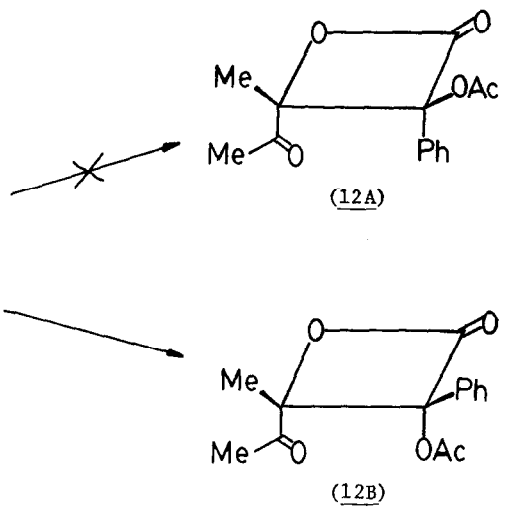


(9) (10) (11)

carbonyl groups in the starting compounds had participated in the reaction. The ^{1}H NMR spectra showed three methyl groups as singlets and absorptions for the five protons of the phenyl moiety. The ^{13}C NMR corroborated the presence of seven aliphatic and six aromatic carbons and one carbonyl group (170.35)[14]. All this data clearly proved that only HCl was lost during the reaction. The above evidence, especially the absence of an acetoxy group in the product, suggested to us an acetoxy participation in the reaction. We suspected that an initial adduct might rearrange at some stage, giving the polycyclic orthoester (11) .

Careful inspection of the oily crude mixture, after filtration of the ammonium salt and before distillation, clearly showed, in the aliphatic region of the ^{1}H NMR spectra, three singlets, but very different from those of (11). Distillation was avoided, a colorless crystalline product (mp 129-30°C) being obtained in 30% yield by simple trituration with methanol[9]. The IR exhibited carbonyl absorption bands at 1840 (β-lactone), 1740(OAc) and 1715($COCH_3$). The ^{1}H NMR showed three singlets at 1.14(CH_3), 2.12(OAc) and 2.41($COCH_3$), in addition to five aromatic protons[14]. This data were clearly indicative of one of the stereoisomeric β-lactone structures (12), presumably formed by a [2 + 2] cycloaddition[2] of acetoxy-phenylketene (4), generated under the reaction conditions[10], to one of the carbonyl groups of biacetyl (10). The high field resonance of the CH_3 group, (1.14 ppm) as compared with the adduct of dichloroketene and acetone (1.79)[11], suggests a cis orientation with respect to the phenyl group, as a consequence of the shielding effect. On the other hand, the deshielding effect on the acetyl group may be attributed to the anisotropy due to the cis orientation with the acetoxy group. On the basis of this evidence, structure (12B) was assigned to this product. It is noteworthy that this compound was not contaminated with any of the isomer (12A), as shown by inspection of the ^{1}H NMR of the crude reaction mixture. We believe that the observed stereoselectivity is a consequence of secondary stabilizing effects between the acyl and the acetoxy groups in the transition state (I) for the [$\pi 2_S + \pi 2_A$] concerted process[12]. The direction of the approach, with the CO of the ketene and the CO of the biacetyl in an "anti" disposition, may be attributed to electrostatic repulsion.

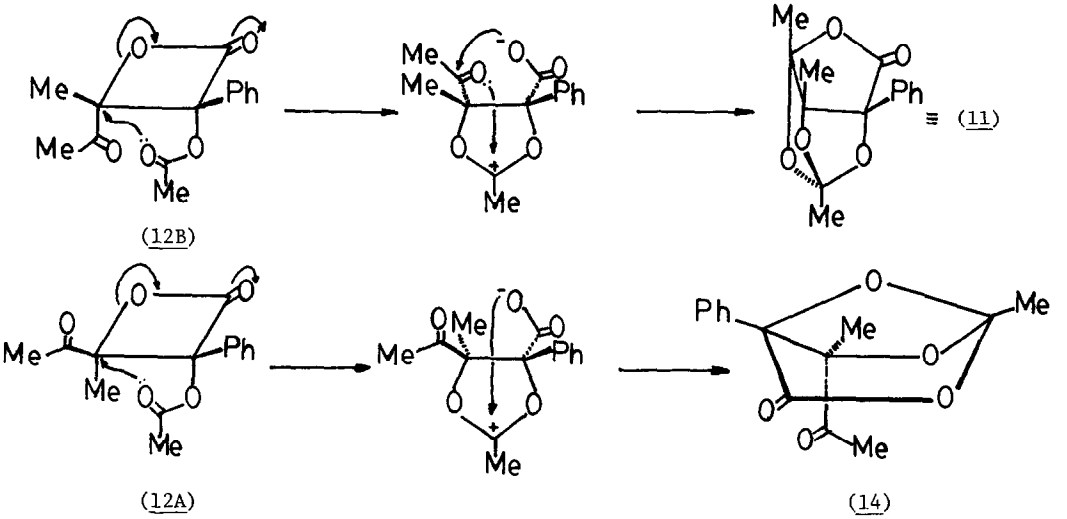




In order to prove that the β-lactone (12B) is an intermediate in the formation of the cyclic orthoester (11), (12B) was subjected to different experimental conditions that we believed might be responsible for the rearrangement. Thus, when a $CDCl_3$ solution of pure (12B) was treated with an excess of triethylamine at room temperature, no transformation took place after 25h, as shown by ^1H NMR analysis. The same result was obtained after treatment with $Et_3N{\cdot}HCl$. The desired transformation did in fact proceed when (12B) was heated above its melting point. Thus, a quantitative yield of (11) was obtained after heating neat (12B) at 130-35°C for 10 minutes. Interestingly, at a lower temperature (125°C) under very high vacuum (0.03 mmHg), the β-lactone (12B) sublimes, no more than 15% of the rearranged product (11) being present in the sublimate. All the above evidence strongly suggests that the initial β-lactone adduct (12B) thermally rearranges, at temperatures slightly above its melting point, to give the polycyclic orthoester (11). A mechanism as depicted in Fig. 1 would explain the formation of (11) exclusively from the β-lactone (12B). Such a mechanism predicts the formation of a different orthoester (14) when starting with the stereoisomeric β-lactone (12A).

To our knowledge, there is only one report in the literature[10] concerning the "in situ" generation of acetoxyphenylketene (4), a (2:1) adduct being isolated in the presence of an imine. No additional studies concerning the stability or reactivity of this ketene were made. Our attempts to isolate acetoxyphenylketene (4), generated by reaction of acetoxymandelyl chloride (9) with Et_3N, gave an intractable gum. On the other hand, benzil proved to be unreactive when (4) was generated in its presence, 81% of the benzil being recovered unchanged. Interestingly, when diphenylketene (1) was generated in the presence of biacetyl (10), no cycloaddition took place, the monoenol derivative of biacetyl (8) (mp 56-57°C) being isolated instead in almost quantitative yield[14]. This difference in reactivity may be due to steric reasons, which preclude the approach of both (1) and (10) in the transition state.

Fig. 1



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9. ^{1}H NMR of the soluble fractions shows additional amounts of this compound. No efforts were made for a quantitative isolation.
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14. Compounds (8), (11) and (12B) gave satisfactory elemental analysis and the following spectroscopic data: (8): ^{1}H NMR δ 2.26 (s, 3H, $COCH_3$), 5.22 (s, 1H, CH), 5.57 (d, J: 2.5 Hz, 1H, vinylic), 5.91 (d, J: 2.5, 1H, vinylic), 7.25-7.50 (m, 10H, Ar); IR 1762 (COO), 1701 cm^{-1} (CO). (11): ^{1}H NMR 1.22 (s, 3H, Me), 1.60 (s, 3H, Me), 1.95 (s, 3H, Me), 7.35-7.45 (m, 5H, Ar); ^{13}C NMR 9.85, 15.83, 17.58 (3xMe), 82.40, 91.25, 108.32, 121.87 (quaternary aliphatic carbons), 126.92, 128.16, 129.09, 130.80 (Ar), 170.35 (CO). (12B): ^{13}C NMR 20.41, 20.84, 24.91 (3xMe), 87.91, 91.44 (quaternary aliphatic carbons), 127.03, 128.86, 129.83, 130.91 (Ar), 165.57, 170.08 and 205.36 (3xCO).

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