aforementioned chloroalanine (0.982 g, 29 mmol) in tetrahydrofuran (30 ml) was added and the mixture was stirred for 2 days. Water (5 ml) was injected, the solvent was removed in vacuo, and the residue was redissolved in hot benzene (3 × 10 ml). The pooled organic phase was washed with water, dried (Na_2SO_4), and evaporated to dryness. On TLC analysis, the crude product was shown to consist of five components: a trace of oil at the solvent front, benzyl N^{α}-benzyloxycarbonyl-L-alaninate (R_f 0.90), the desired ester (R_f 0.58), unreacted dibenzyl malonate (R_f 0.40), and monosodium dibenzyl malonate (R_f 0.04). Chromatography over silica gel using benzene gave a pure fraction (0.326 g), as well as another cut contaminated with some dibenzyl malonate (0.438 g): ν_{max} 3540 (NH), 3065, 3040 (aromatic CH), 2960 (aliphatic CH), 1800, 1740 (CO), and 697 cm^{-1}; δMe_4Si 7.35 (aromatic), 5.90 (NH), 5.2 ($CH_2C_6H_5$ and $OCH_2C_6H_5$), and 4.80 (CH); $[\alpha]^{20.0}D$ 0.0° (c 1); mass spectrum m/e 595.2148 ($C_{35}H_{33}NO_8$, parent ion), 460 (loss of $C_6H_5CH_2OCO$), 396 (loss of $C_6H_5CH_2OH$), 108 ($C_6H_5CH_2OH$), and 91 (C_6H_7).

Benzyl N^{α}-Benzyloxycarbonyl-2-methyleneglycinate (V). A solution of benzyl N^{α}-benzyloxycarbonyl-3-chloro-L-alaninate (0.180 g, 5.1 mmol) in tetrahydrofuran (3 ml) was added to a suspension of sodium hydride (50% in mineral oil, 0.031 g, 6.0 mmol) in tetrahydrofuran (5 ml) and stirred for 3 h. The solvent was removed in vacuo and the residue was redissolved in benzene (10 ml). The organic phase was washed with water, dried (Na_2SO_4), and evaporated to leave an oily residue. Chromatography of a benzene solution over a silica gel column gave the pure product as an oil (0.082 g, 52%): R_f 0.38; ν_{max} 3420 (NH), 3045, 3030 (aromatic CH), 2960 (aliphatic CH), 1740, 1720 (CO), 1635 (C=C), and 697 cm^{-1}; δ_{Me_4Si} 7.3 (aromatic), 6.20 (=CH), 5.75 (=CH), J = 1 Hz, 5.09 ($CH_2C_6H_5$), and 5.02 ($OCH_2C_6H_5$); ν_{max} 245 nm (ε 6600); mass spectrum m/e 311.1278 ($C_{18}H_{17}NO_4$, parent ion), 220 (loss of $C_6H_5CH_2$), 176 (loss of $C_6H_5CH_2OCO$), 107 ($C_6H_5CH_2O$), and 91 (C_6H_7).

DL-γ-Carboxyglutamic Acid (I). A. From Hydrogenolysis of Tribenzyl 3-Benzyloxycarbonylamino-DL-1,1,3-propanetricarboxylate. A solution of the aforementioned tribenzyl ester (0.260 g, 0.9 mmol) was dissolved in methanol (50 ml), 10% palladium on charcoal catalyst (0.060 g) was added, and hydrogen was bubbled through the suspension for 2.5 h at room temperature. At this time the reaction was judged complete both by monitoring the rate of precipitation of $BaCO_3$ and the disappearance of starting ester by TLC analysis. The filtered solution was evaporated to leave a clear residue, which on lyophilization afforded a white powder (0.060 g, 72%): mp 90–92 °C, followed by evolution of a gas at 114 °C; ninhydrin positive; $[\alpha]^{22.5}D$ 0.0° (c 1); no observable chiroptical property with 2-methoxy-2,4-diphenyl-3(2H)-furanone.[17] Chromatography of an aqueous solution of the synthetic amino acid at pH 3.25 on a Dow X-50 column gave the same retention time as that of authentic natural γ-carboxyglutamic acid. The latter compound was obtained by the hydrolysis of prothrombin. This value was different from that observed for glutamic acid or alanine. Hydrolysis of a synthetic sample with 6 N HCl for 4 h at 110 °C formed glutamic acid, identical in all aspects with DL-glutamic acid. The thiohydantoin derivative possessed the same R_f values as observed for natural γ-carboxyglutamic acid thiohydantoin.

B. From the Reaction of Benzyl N^{α}-Benzyloxycarbonyl-2-methyleneglycinate with Dibenzyl Malonate. A suspension of sodium hydride (50% in mineral oil, 0.014 g) in tetrahydrofuran (5 ml) under a nitrogen atmosphere was stirred with dibenzyl malonate (0.072 g) for 5 min, then the methylene ester V (0.062 g) was added in tetrahydrofuran (3 ml). After 2 h at room temperature, the solution was refluxed for an additional 2 h. The reaction was treated as previously described to yield DL-γ-carboxyglutamic acid (0.096 g), identical with the previous sample.

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Registry No.—I, 56271-99-9; II, 21209-51-8; III, 55822-82-7; IV, 60064-83-7; V, 59524-07-1; dibenzyl malonate, 15014-25-2.

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Preparation and Grignard Reactions of 2-Benzoyl-4,4-dimethyl-2-oxazoline

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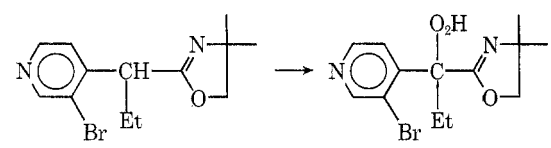
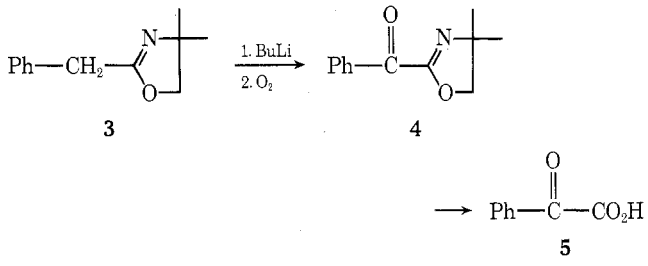
The autoxidation of organic compounds containing acidic carbon–hydrogen bonds is a well-known reaction.[1] For example, Gersmann and Bickel report that high yields of α-hydroperoxy esters are formed when oxygen is bubbled through cold solutions of esters in the presence of a base.[2] However, with methyl phenylacetate, the expected hydroperoxy ester was reported as a minor product, apparently undergoing further reaction to yield as the major product the α-keto ester, methyl phenylglyoxylate, along with some methyl mandelate. Gersmann and Bickel demonstrated that for ketones and nitriles the α positions are also susceptible to autoxidation and suggested that the reaction should be general for other compounds containing similarly activated acidic carbon–hydrogen bonds.

The extensive work of Meyers and co-workers with 2-alkyl-2-oxazolines has demonstrated the utility of these compounds for the protection and synthesis of carboxylic acid derivatives.[3] Since the protons adjacent to the ring in the 2-alkyl substituent are activated by the oxazoline, it seemed likely that these compounds, like those studied by Gersmann and Bickel, might be susceptible to autoxidation. Indeed, oxidation of 1 has been reported to give 2 in high yield.[4] It was hoped that autoxidation of appropriate 2-alkyl-2-oxazolines might provide a useful route to the previously unreported 2-acyl-2-oxazolines which would have potential utility as synthetic reagents.



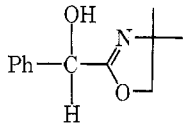
1 2

The choice of 2-benzyl-4,4-dimethyl-2-oxazoline (**3**) for initial autoxidation studies was based upon its close structural analogy with methyl phenylacetate. When a cold solution of the lithio derivative of **3** in tetrahydrofuran (THF) was treated with oxygen, rapid oxidation occurred, and 2-benzoyl-4,4-dimethyl-2-oxazoline (**4**) was produced as the major product.



3 **4** **5**

Compound **4** forms a crystalline phenylhydrazone derivative, and undergoes acidic hydrolysis to phenylglyoxylic acid (**5**). Reduction of **4** with sodium borohydride gives the carbinol **6**, which can be hydrolyzed to mandelic acid. The compound



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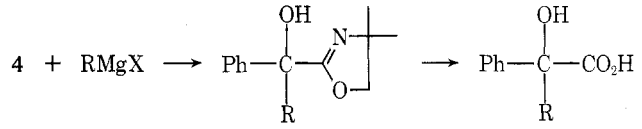
6 was identified as a minor product from the autoxidation reaction.

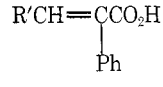
The potential synthetic utility of 2-acyl-2-oxazolines is suggested by the preparation of 2-substituted mandelic acid derivatives, **8**, by reaction of **4** with Grignard reagents followed



7 **8**

by hydrolysis of the intermediate carbinols, **7**. The results of this study are summarized in Table I.

Two hydrolysis methods modeled on those used by Meyers were used in the conversion of **7** to **8**, with the method of choice depending upon the nature of the group R. Direct hydrolysis of **7** with refluxing hydrochloric acid (6 N) was the simplest method and was used where applicable. However, in two of the cases this method proved unsatisfactory, since acidic hydrolysis was accompanied by dehydration to **9**. In the case of



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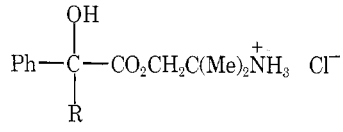
7a this led to atropic acid, **9** (R′ = H), which partially dimerizes to isoatropic acid under the reaction conditions,[5] while for **7b** a mixture of *cis*- and *trans*-2-phenyl-2-butenoic acids, **9** (R′ = Me), was obtained and separated by the method of Carpino.[6] Dehydration was not a serious problem in the hydrolysis of **7c** unless heating with acid was prolonged well beyond the time required for the desired hydrolysis.

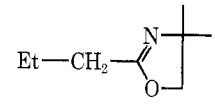
An alternative hydrolysis method which avoids dehydration involved the cleavage of the oxazoline ring under milder conditions by warming at 50–60 °C in 6 N hydrochloric acid for 15–30 min. The hydrolysis was completed by heating the resulting amino ester hydrochloride, **10**, in refluxing 20% NaOH in methanol–water.[3b]



10

The ease of hydrolysis of the carbinols, **7**, as one might expect, decreases as the bulk of R is increased. For example, **7a** is rapidly opened to **10** by 6 N HCl at 50–60 °C, while substantial quantities of the oxazoline are recovered under these conditions for **7c**. Indeed, an attempt to extend this reaction to **7f** failed. Although **7f** was obtained from the reaction of *tert*-butylmagnesium chloride with **4**, the bulky *tert*-butyl group prevented hydrolysis of the oxazoline under even rather vigorous conditions. The oxazoline was finally consumed by heating under reflux for 48 h in 6 N HCl, but under these conditions no acidic products were obtained, so if **8f** is formed, it does not survive under the reaction conditions.

The choice of **3** for the initial autoxidation studies proved to have been a fortuitous one, since subsequent attempts to form acyloxazolines from simple alkyloxazolines such as **11**



11

have been unsuccessful. It appears that the oxazoline ring alone provides insufficient activation to promote smooth autoxidation, and the additional influence of the aryl group is required. Thus, while it appears that the 2-acyl-2-oxazolines may be useful reagents for organic synthesis, autoxidation is of limited value in their preparation.

Experimental Section

Ir spectra were run as neat liquids or Nujol mulls using a Perkin-Elmer 710B spectrophotometer. NMR spectra were run in $CDCl_3$ with the Hitachi Perkin-Elmer R20 spectrometer, and chemical shifts are reported as δ in parts per million relative to tetramethylsilane. Melting points were obtained with the Mel-Temp apparatus and are uncor-

Table I. Preparation of α-Substituted Mandelic Acids from 2-Benzoyl-4,4-dimethyl-2-oxazoline

Grignard reagent	Grignard product[a] mp, °C	Registry no.	Hydrolysis method[b]	Overall yield of 8, %	Registry no.
MeMgI	**7a** (53–55)	60031-29-0	B	86	515-30-0
EtMgBr	**7b** (45–46)	60031-30-3	B	82	35468-69-0
i-PrMgBr	**7c** (77–78)	60031-31-4	A	75	15879-60-4
PhMgBr	**7d** (85–87)	60031-32-5	A	85	76-93-7
PhC≡CMgBr	**7e** (141–143)	60031-33-6	A	90	60031-34-7
t-BuMgCl	**7f**[c]	60031-35-8	A	0	

[a] All new compounds gave satisfactory analysis for C, H, and N. [b] Method A involves heating **7** in refluxing 6 N HCl; method B involves warming **7** for 15–30 min in 6 N HCl at 50–60 °C followed by heating in refluxing 20% NaOH in MeOH–H_2O. [c] An oil, bp 98–100 °C (0.15 Torr).

rected. Analyses were performed by Clark, Means, and Perkins Microanalytical Laboratory, Urbana, Ill.

2-Benzyl-4,4-dimethyl-2-oxazoline (3). The method of Wehrmeister was used.[7] A mixture of 272 g (2.0 mol) of phenylacetic acid and 178 g (2.0 mol) of 2-amino-2-methyl-1-propanol in 500 ml of xylene was heated to maintain gentle reflux using a 35-cm Vigreux column and a Dean-Stark trap. After 30 h the calculated amount of water had been removed. The solution was cooled, washed with 10% $NaHCO_3$ and with brine, dried over K_2CO_3, and distilled. The product was 295 g (78%) of colorless liquid: bp 132–134 °C (19 Torr); NMR δ 7.22 (s, 5 H), 3.79 (s, 2 H), 3.52 (s, 2 H), 1.20 (s, 6 H); ir 1665 cm^{-1}.

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.76; H, 7.72; N, 7.34.

2-Benzoyl-4,4-dimethyl-2-oxazoline (4). A solution of 69 g (0.37 mol) of **3** in 1000 ml of dry THF was cooled in dry ice–acetone to −77 °C and stirred under N_2 while 150 ml of *n*-butyllithium (2.45 M in hexane) (0.37 mol) was added over 60 min. The addition funnel was removed (*Caution:* if the funnel is left in place, residual butyllithium may cause detonation during introduction of oxygen) and replaced by a gas dispersion tube extending below the surface of the mixture. Dry oxygen was bubbled into the mixture at a rate such that the temperature remained below −70 °C, and the partially insoluble lithio derivative of **3** dissolved over 50 min. Introduction of oxygen was continued at −77 °C for an additional 3 h, then the solution was treated with 200 ml of 10% NH_4Cl and 1000 ml of ether. The organic layer was separated, washed with brine, and dried over K_2CO_3. The solvent was evaporated, and the residue was dissolved in 500 ml of hexane and allowed to stand for 2 days. A white solid precipitate, 14 g, was filtered off and washed with hexane. The combined filtrate and wash was evaporated, and the residue was distilled to give 44.8 g (60%) of a faintly yellow liquid, bp 104–108 °C (0.1 Torr). The analytical sample was further purified by chromatography on silica gel and distillation as a colorless liquid: bp 102–103 °C (0.1 Torr); NMR δ 7.1–8.3 (m, 5 H), 4.04 (s, 2 H), 1.38 (s, 6 H); ir 1670, 1630 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.82; H, 6.54; N, 6.70.

Treatment of an ethanol solution of **4** with 1 equiv of phenylhydrazine gave, after cooling and recrystallization from ether–pentane, the phenylhydrazone as white needles, mp 90–91 °C.

Hydrolysis of **4** by method A (see below) gave 86% of phenylglyoxylic acid which was identical with an authentic sample.

Reduction of 4 with Sodium Borohydride. A solution of 10.15 g (0.05 mol) of **4** in 20 ml of 95% ethanol was added dropwise at 0–5 °C to a stirred solution of 1.9 g (0.05 mol) of $NaBH_4$ in 50 ml of 95% ethanol. After stirring for 2 h at 0 °C, the solution was diluted with an equal volume of water and extracted with three 50-ml portions of ether. The organic extract was washed with brine, dried (Na_2SO_4), and evaporated to yield 10.02 g (98%) of the carbinol **5**. Recrystallization from acetone–hexane gave white crystals: mp 78–79.5 °C; NMR δ 7.1–7.6 (m, 5 H), 5.72 (br s, 1 H), 5.29 (s, 1 H), 3.82 (s, 2 H), 1.16 (s, 6 H); ir 3150, 1655 cm^{-1}.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.21; H, 7.40; N, 7.13.

Hydrolysis of **5** by method B (see below) gave 63% of mandelic acid identified by comparison with an authentic sample.

Reaction of 4 with Grignard Reagents. In a typical reaction, a solution of 30 mmol of the Grignard reagent in 25 ml of dry ether was prepared in the usual manner. To the stirred Grignard solution under N_2 was added, at a rate to maintain moderate reflux, a solution of 20 mmol of **4** in 40 ml of ether. When addition was complete the mixture was stirred under reflux for 1–2 h and was then treated carefully in the cold with 20 ml of 20% NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with three 50-ml portions of ether. The ether solutions were combined, washed with brine, dried (Na_2SO_4), and evaporated. The carbinols, **7**, could be isolated in yields of 85–95%, but usually the crude mixture was hydrolyzed without further purification using one of the methods below. In the case of *tert*-butylmagnesium chloride, the reagent was generated in THF, and the yield of **7f** was only 48%.

Hydrolysis Method A. The oxazoline (20 mmol) or the crude product from the Grignard reaction above was dissolved in 20 ml of HCl (6 N) and heated under reflux. Times required for complete hydrolysis varied from 1 to 4 h. The mixture was cooled and extracted with 50 ml of ether, and the ether solution was washed with brine, dried (Na_2SO_4), and evaporated. The products were recrystallized from cyclohexane.

Hydrolysis Method B. The oxazoline (20 mmol) or the crude product from the Grignard reaction was treated with 6 ml of 6 N HCl and warmed to 50–60 °C for 15–30 min. The resulting mixture was treated with a solution of 10 g of NaOH in 50 ml of methanol–water (1:1) and heated under reflux for 1–2 h. The methanol was evaporated and the aqueous solution was acidified to Congo red with HCl (concentrated). The mixture was extracted with three 50-ml portions of ether, and the ether solution was washed with brine, dried, and evaporated. The products were recrystallized from cyclohexane.

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Registry No.—**3**, 1569-08-0; **3** lithio derivative, 60031-36-9; **4**, 60031-37-0; **4** phenylhydrazone, 60031-38-1; **5**, 611-73-4; MeI, 74-88-4; EtBr, 74-96-4; *i*-PrBr, 75-26-3; PhBr, 108-86-1; PhC≡CBr, 932-87-6; *t*-BuCl, 507-20-0.

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Oximation of 3,5-Dimethyl-4-piperidones. Configurations and Conformations of the Adducts

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Isolated examples of changes of configuration and conformation during oximation of hexacyclic ketones substituted α,α' to the carbonyl group have been observed and according to Johnson[1a,b,c] attributed to the $A^{(1-3)}$ interaction due to introduction of the hydroximino group. *cis*-2,6-Dimethylcyclohexanone, for example, gives predominantly the oxime conformation with the two methyl groups in an axial orientation[2] signifying that reaction occurs on a ketone which although less stable conformationally is less crowded sterically; previously[1c] this oxime has been shown to epimerize very slowly to trans compound. 1-Methyl-*cis*-3,5-diphenyl-4-piperidone, on the other hand, gives only the oxime where the phenyl groups are in an orientation trans to each other.[3] The Mannich base character of piperidones makes them able to epimerize their α,α' positions through a keto–enol equilibrium more easily than other ketones or their β,β' positions through a reverse Mannich reaction.[4,5] In the latter example[3] oximation occurs on 1-methyl-*trans*-3,5-diphenyl-4-piperidone formed by prior epimerization of the cis ketone in the reaction medium.

It would seem then that for piperidones configurational rather than conformational changes would be more facile. However, in a single instance, that of 1-methyl-*cis*-2,6-diphenyl-*cis*-3,5-dimethyl-4-piperidone, it has been reported that the product of reaction has a twist-boat conformation with no suggestion of epimerization.[6]

With a view to clarifying the situation, we have made a more detailed examination of the oximation of *cis*-3,5-dimethyl-