Concerning 2-Carbomethoxytropinone*

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Received June 25, 1957

Racemic 2-carbomethoxytropinone is obtainable by the partial saponification of 2,4-dicarbomethoxytropinone and, more conveniently, by the condensation of monomethyl β-ketoglutarate, got from β-ketoglutaric anhydride, with succindialdehyde and methylamine. 2-Carbomethoxytropinone can conceivably exist in three racemic and six optically active forms. Of these only one has been obtained heretofore. The configurational relation of d-(2-carbomethoxytropinone) and its E antipode to 1-cocaine is established by the Kiliani chromic acid oxidation of pseudoecgonine methyl ester to the former. Previous methods of preparing racemic 2-carbomethoxytropinone, the properties of 2,4-dicarbomethoxytropinone, and incidental experimental data are discussed.

In any synthetic scheme for cocaine (II) and its stereoisomers, 2-carbomethoxytropine (I) is an obvious and probably the best key intermediate and has indeed been used to prepare d- and l-cocaine and racemic pseudococaine. In connection with the synthesis of the other two isomers, allococaine and allopseudococaine, unreported until recently, relatively large amounts of this β-ketoester were needed, and it was accordingly desirable to ascertain the most efficient method of its preparation.

Of the four synthetic methods recorded, one (Sequence A) is rather involved, and the cyclization of 1-methyl-2,5-dicarboethoxypyrrolidine (III, R = C6H5) to 2-carboethoxytropinone (IV, R = C6H5) difficult. Another (Sequence B), in principle the simplest, is reported to give only a twenty per cent yield of product. Hence, only the remaining two (Sequences C and D), which are relatively simple and claimed to proceed in good yield, came into consideration.

On the basis of the yields reported and the availability of the starting materials Sequence C seemed preferable. Tropinone (V), the components for the Robinson Synthesis of which are now obtainable commercially (see Experimental), can be made in high yield (75%) and, according to Preobrajenski, is readily convertible (70-80%) by sodium or potassium and dimethyl carbonate in boiling benzene or xylene to 2-carbomethoxytropinone. It was here found, however, that, although the reported yields of tropinone are not exaggerated, this base is thus transformed to 2-carbomethoxytropinone only in rather low yield (~35%). For such a process many side reactions are conceivable, and in fact some or all of them do occur and produce large amounts of resinous by-products.

Certain variations of the reaction were also tried. Substituting sodium methoxide in toluene did not alter the outcome appreciably. Sodium methoxide in a small volume of methanol gave a somewhat lower yield. By increasing the relative amount of methanol and prolonging the time of reaction correspondingly the product is markedly reduced and

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

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much unreacted tropinone is recoverable, excess solvent reversing the reaction presumably.  

D. (CH₃O₂C₂H₅)₂CO

\[ \xrightarrow{2 \text{KOH}} \text{CH}_{2}-\text{COOK} \]
\[ \xrightarrow{\text{CH}_2\text{OH}^-} \text{CH}-\text{COCH}_3 \]

E. (CH₃O₂C₂H₅)₂CO

\[ \xrightarrow{\text{CH}_2\text{NH}_2\text{HCl}^-} \text{NCH}_3 \]
\[ \xrightarrow{\text{CO}_2\text{H}_3^-} \text{VI} \]

F. O=C\]
\[ \xrightarrow{\text{CH}_2\text{OH}^-} \text{CH}_2-\text{COCH}_2 \text{H} \]

In these circumstances Willstätter's synthesis² (Sequence D) or some modification thereof promised to be more satisfactory. The chief difficulty of Willstätter's method lies in preparing the pure dipotassium salt of monomethyl \( \beta \)-ketoglutarate, the yield being less than 50%. Although it was found that treatment of dimethyl \( \beta \)-ketoglutarate with methanolic potassium hydroxide affords a high yield of somewhat impure dipotassium salt, also convertible to 2-carboxyethoxytropinone, no essential improvement of Willstätter's over-all yield (～30%) of the keto ester was realized in this manner. The formation of other potassium salts of lesser solubility and the ease with which \( \beta \)-ketoglutarates undergo self-condensation in the presence of basic catalysts¹⁴ are probably the chief factors contributory to the low harvest of pure dipotassium salt. 

By a reversal (E) of Willstätter's sequence one might hope to avoid some or all of the foregoing complications. Indeed the Robinson Synthesis of 2,4-dicarboxomethoxytropinone (VI) appears to proceed in high yield; and its partial saponification is, moreover, effected more readily than that of the parent compound. 

This procedure is, however, tedious, and another variation (F) of Willstätter's synthesis, consisting in the use of monomethyl \( \beta \)-ketoglutarate as its methylammonium salt, was therefore investigated. \( \beta \)-Ketoglutaric anhydride (VII),¹² which was obtained in excellent amount by a modification of Kaushall's procedure, is converted to the requisite monomethyl \( \beta \)-ketoglutarate by dissolving it in methanol. Although the optimum conditions for its condensation subsequently with succindialdehyde and methylamine were not determined, racemic 2-carboxyethoxytropinone was thus obtained in satisfacory quantity (52-59%). Unlike the condensation, discussed in more detail below, of dimethyl \( \beta \)-ketoglutarate this proceeds with fewer side reactions in alkaline solution. For both simplicity and yield this sequence is very likely superior to all others presently known and probably represents also a convenient means of synthesizing certain derivatives of cycloheptane.

2,4-Dicarboxomethoxytropinone (VI) which may be the first isolated dicarboxalkoxy derivative of tropinone is a sufficiently unusual compound to merit some description. Its formation in high yield is contingent on the use of methylamine as its hydrochloride or similar salt; the greater the proportion of free amine used, the larger the quantity of dark, polymeric by-products. In his classical article on the synthesis of tropinone, Robinson prepared a solution of the 2,4-dicarboxoethanol by a similar procedure. His use of free methylamine may account for the apparent low yield of tropinone obtained therefrom by acid hydrolysis.¹³ The large number of isomers, both geometric and tautomeric, which are possible for compounds of such structure, should, partly because of the basic nitrogen atom and partly because of their presumably similar stabilities, be readily interconvertible; and the failure of this representative to exhibit either reproducible or sharply defined physical properties is therefore not surprising. Anhydrous 2,4-dicarboxomethoxytropinone seems to exist only as a liquid, but two possibly distinct modifications of a solid hemihydrate, \( \text{C}_6\text{H}_2\text{H}_3\text{N}_2\text{O}_7\cdot1/2\text{H}_2\text{O} \), one white (m.p. 82.5–84°) and the other tan (m.p. 88–91°), were obtained. These forms, which precipitated slowly and appeared to be only partly crystalline, have nearly indistinguishable infrared spectra in Nujol. The binoxalate salt seems to exist in two modifications also, one being obtainable directly from the hemihydrate and melting about 146°, the other from the newly liberated anhydrous base and melting about

¹⁰ The strength of the indicated bonds, NaO—H and NaO—R, being different, one need not expect sodium alkoxydes or enolates to effect acid cleavage of \( \beta \)-keto esters. While no ester of acetoacetic acid itself has seemingly been obtained therefrom by acid hydrolysis, excess methanol lowers the yield in such reactions.


155°. In aqueous sodium sulfate or in aqueous acetone equivalent amounts of 2,4-dicarbomethoxytropinone and sodium hydroxide react slowly to give a yellow precipitate which may be the sodium salt of the half ester and which is decomposed by mineral acids to carbon dioxide and racemic 2-carbomethoxytropinone.

Although 2-carbomethoxytropinone (I) has three asymmetric carbon atoms and hence, theoretically, four racemic forms, the formation of only two of these (IX and X and their antipodes) is, of course, to be expected. Another kind of racemate, that of the enol form (XI and its antipode), is also possible and the benzoyl derivative thereof has indeed been prepared. According to Willstätter, racemic 2-carbomethoxytropinone melts at 111° and its monohydrate at 100°; but whether these two forms have the same molecular constitution has not been established before. Neither he nor Preobrashenski looked for or found more than one racemic form.

None of the numerous batches of anhydrous racemic 2-carbomethoxytropinone prepared in this investigation melted sharply or as high as 111°. An analytically pure sample, generated from the pure picrate and then sublimed, melted at 103.5–104.6°; and chromatography of a somewhat less pure sample furnished material which melted no higher. In one instance needles melting at 104–107.4° were obtained. Furthermore, no monohydrate melting at or near 100° could be isolated. Indeed the only analytically pure hydrated form obtained in this work crystallized from aqueous acetone or from aqueous methyl acetate as colorless needles melting at 93–96° and having the composition of a dihydrate. Another form (m.p. 81.5–86°), which appeared to be largely a monohydrate, was also obtained from aqueous acetone; and from aqueous methanol a granular modification slowly separated which melted at 97.5–98° and had a composition approximating that of a trihydrate. From all of these forms the anhydrous base can be obtained by sublimation or distillation in high vacuum. It is noteworthy that Preobrashenski reported the hydrate to melt at 96–98°.

These indications that racemic 2-carbomethoxytropinone, as usually obtained, is a somewhat variable mixture of easily interconvertible epimers or tautomers were supported by the isolation of two picrate salts. One, which is granular or powdery and melts about 167°, is got from acetone solution; the other, which crystallizes well and melts at 176°, separates from solutions in methyl alcohol. One form may be converted to the other merely by recrystallization from the other solvent. Two binoxalate salts were also found. One crystallizes from water as a sesquihydrate, is readily dehydrated, and melts about 135° with decomposition. The other crystallizes from water as a dihydrate, is less readily dehydrated, and melts at 145° with little or no decomposition. Both binoxalates regenerate one and the same form of racemic 2-carbomethoxytropinone.

The inhomogeneity of anhydrous 2-carbomethoxytropinone was confirmed by infrared measurements. In chloroform solution the base absorbs in regions characteristic of both keto and enol structures. On the other hand the dihydrate in Nujol gives no evidence of the presence of the keto form; and, similarly, 2,4-dicarbomethoxytropinone hemihydrate appears to exist exclusively as the enol. The ultraviolet spectra of the two esters in absolute alcohol demonstrate the predominance of the enol form of such compounds in polar solvents, and a molecular model of 2-carbomethoxytropinone suggests that the bridged-ring structure characteristic of the tropane alkaloids contributes to the stability of this tautomer. One concludes that, although this β-keto ester in the anhydrous state is usually obtained as a mixture of ketone (IX and/or X and their optical antipodes) and enol (XI and its antipode), it exists largely or entirely as the enol when hydrated or dissolved in a hydroxylic solvent. Since Willstätter employed methanol which favors the enol form to recrystallize the base, the high and sharp melting point reported by him may represent that of the pure anhydrous enol.

2-Carbomethoxytropinone was readily resolved by recrystallizing its L- and D-bitartrates from water. The L-bitartrate dihydrate has a specific rotation in water of +15.4° ([M]D20 + 5898 ± 40). Recovered from the L-bitartrate, d-(2-carbomethoxytropinone) has a specific rotation in methanol of +18.3°. Like the racemic modification it crystallizes in the presence of water as a dihydrate and gives, seemingly, two picrate salts. It melts higher and more distinctly at 108.5–109.5° (Table I).

| TABLE I |
| Melting Points of 2-Carbomethoxytropinones and Some of their Salts |
|----------|------------------|------------------|
|          | Racemic          | d- or l-         |
| Anhydrous Base | 103.5–104.5° (111°) | 108.5°–109.5° |
| Dihydrate    | 93–96° (100°)    | 98.5–101.5°     |
| Picrate      | 167–168° and 176° | 174 and 176.5°  |
| Binoxalate   | 137° and 145°    | 142°            |
To ascertain its configurational relation to the naturally occurring, parent alkaloid, l-cocaine, the oxidation of l-ecgonine methyl ester (XIII) and its d-epimer,\(^{14}\) d-pseudoecgonine methyl ester (XIV), was undertaken.

Although catalytic dehydrogenation, dehydrobromination, and photochemical oxidation experiments were unsuccessful, a small yield of the keto ester as the \(d\)-antipode was at length obtained by oxidizing either epimer in acetone with Kiliani's chromic acid solution.\(^{15,16}\) Accordingly, \(d\)-(2-carbobromoxytropinone) is derived configurationally from \(l\)-cocaine (XII)\(^{16}\) and must therefore have the structures, IX-XI, rather than their mirror images.\(^{17}\) The low yield of the \(\beta\)-keto ester may be owing both to the resistance of equatorial hydroxyl groups\(^{18,19}\) to oxidation and to the ease with which this product is further oxidized.\(^2\)

Inasmuch as racemic 2-carbobromoxytropinone has been reduced both with sodium amalgam\(^2\) and with catalytic hydrogen\(^1\) to the two possible configurations of the \(C_\text{r}\)-hydroxyl group, which have been converted in turn to the four possible racemic ecgonines,\(^3\) the resolution of racemic 2-carbobromoxytropinone just described is tantamount to the direct synthesis of all the optically active cocaine isomers, known and unknown. Indeed, catalytic reduction of the \(d\) antipode in aqueous acetic acid furnished what is presumably alloecgonine methyl ester\(^1\) which was isolated as the optically active hydroacetate.

The results here set forth are in essential agreement with the long and excellent memoir of Mannich concerning the preparation and properties of the analogous 1,2,6-triaryl-3,5-dicarbalkoxy-4-piperidones from which were obtained "open" tropine, cocaine, and their derivatives.\(^{19}\) A few of the similarities of and the differences between these two similar classes of compounds are noteworthy. Mannich likewise obtained better yields of keto diesters by using methylamine as the hydrochloride rather than as the free base, noted the instability of such compounds and their salts in hydroxyl solvents, and resolved 1,2,6-trimethyl-4-keto-3-carbobromoxy Piperidine by means of the bitartrate salts. On the other hand, he was unable to obtain this last compound in good yield by partial saponification and found that catalytic hydrogenation of its hydrochloride resulted in the formation of racemic \(\beta\)-hydroxy esters.\(^{20}\)

Miscellaneous Observations. Tropinone, prepared approximately according to the procedure of Keagle and Hantung,\(^7\) was contaminated by a small quantity of a high-boiling, liquid by-product, which is presumably the other possible form of 2,5-diacetonyl-1-methylpyrrrolidine.\(^8\) It was characterized as its pircate and \(\text{bis-p-nitrophenylhydrazone.}\)

Reduced with ethereal lithium aluminum hydride, racemic 2-carbobromoxytropinone gave a mixture which could not be readily purified. One of the products, isolated as the pircate, appeared to be racemic anhydroecgonine methyl ester.

Dimethyl \(\beta\)-keto glutarate was prepared in 65\% yield by adding dry methanol to the mixture resulting from the reaction of anhydrous citric acid and fuming sulfuric acid.\(^{21}\) Distillation had the expected effect on the keto-enol equilibrium. The action of fuming sulfuric acid on dimethyl citrate produces this ester directly in small yield.

Exploratory experiments to determine whether racemic 2-carbobromoxytropinone can be got from 2,5-dietoxytetrahydrofuran or succindialdehyde, methylamine, and the readily available methyl acetocetate resulted, according to the conditions, in two seemingly new compounds, \(\text{C}_{11}\text{H}_{18}\text{NO}_4\) (m.p. 166\(^\circ\)) and \(\text{C}_{11}\text{H}_{17}\text{NO}_4\) (m.p. 119-124\(^\circ\)), which were rather laboriously separated from large quantities of viscous by-products. The former is basic and gives a well-defined binolalate; the latter is neutral.

EXPERIMENTAL\(^22\)

Materials. Carbide and Carbon 2,5-dietoxytetrahydrofuran (\(\alpha\)-\(1.4208; \text{reported.}\)^{21} \(\alpha\) 1.4164), Charles Pfizer and Co., Inc. (1934).

(20) 2-Carbobromoxytropinone hydrochloride is under similar conditions nearly inert (unpublished observations of the author).

(21) Cf; B. R. Baker, R. E. Schaub, M. V. Querry, and J. H. Williams, \(J. \text{Org. Chem.}, \text{17}, \text{97 (1952).}\)

(22) All melting points recorded herein are corrected and were observed in Pyrex glass capillaries.

(23) J. Fakstorp, D. Raleigh, and L. E. Schneipp, \(J. \text{Am. Chem. Soc.}, \text{72}, \text{809 (1950).}\)
2-CARBOMETHOXYPINONE

β-ketoglutaric acid (m.p. 133°), Fisher sodium methoxide, and Fisher methyamine hydrochloride (C.P.) were used without further purification. Eastman Kodak dimethyl carbonate was dried over potassium carbonate and distilled from silver carbonate: b.p. 88°/760 mm., n\textsubscript{D}^2 1.3684 (reported: n\textsubscript{D}^2 1.3687). L-Tartaric acid (the naturally occurring, dehydrorotatory tartaric acid, also known as L-threonic acid) was a Mallinckrodt Chemical Works product; D-tartaric acid was obtained from Aldrich Chemical Company, Milwaukee, Wis.

Tropinone. 2,5-Diethoxytetrahydrofuran (32 g, 0.200 mole) was stirred 15 min. under nitrogen with 0.2N sulfuric acid (100 ml.) and kept 4–5 hr. under nitrogen with occasional agitation. The homogeneous solution was then stirred with BaCO\textsubscript{3} (8 g.) until nearly neutral and the barium salts were added sodium chloride and the mixture was extracted with cold water (50 ml.) and kept on keeping overnight. It was recrystallized by dissolving in hot acetone, cooling, adding a little water, and evaporative distillation. After a week Fractionator was taken up in ether (100 ml.) and was collected and washed. The filtrate from silver carbonate: b.p. 111–112°/760 mm., m.p. 15–20° (15–20° during 1.5 hrs. after two distillations tropinone (40 g., 72%), m.p. 39–43.8°, b.p. 107–110°/23 mm. The base, initially colorless, acquires a brown coloration in a matter of hours. Inasmuch as the base is scarcely darker after a month than after the last solvent: slender prisms, m.p. 113–114° (softening at 111°). Evaporative distillation of 90/1 (m/m.) of the high-boiling residue from the first distillation (above) gave a small amount (~0.6 g.) of colorless, basic oil which became red on keeping. Prepared in and purified from methanol, its bis-p-nitrophenylhydrazone was obtained as small, yellow-ish-orange, stout prisms having hexagonal faces, m.p. 88°/760 mm.,[6] n\textsubscript{D}^2 1.5277, 133°/1 atmosphere.

The reaction of tropinone with dimethyl carbonate. (a) Using sodium in xylene. To a warm solution of tropinone (3.6 g.) and dimethyl carbonate (6.1 ml.) in dry xylene (7.0 ml.) was added sodium (0.70 g.) in small pieces; and the reaction mixture, protected against moisture and carbon dioxide, heated quickly to boiling. The initially nearly colorless solution which gradually darkened during the subsequent heating, was refluxed 20 min., the sodium dissolving with effervescence within about 13 min. After cooling to 0°, the mixture was extracted with cold water (2 × 10 ml.), the aqueous extracts mixed with ammonium chloride (2.0 g.) and extracted with chloroform (5 × 50 ml.), and the dried extracts concentrated in vacuo to a brown oil (5.8 g.). Mixed with water (1.5 ml.) at 0° this gave the crude hydrate (3.2 g.) which was collected after several hours and which darkened on keeping overnight. It was recrystallized by dissolving in hot acetone, cooling, adding a little water, and rubbing to induce crystallization. The yellowish-brown crystals were then freed of remaining gummy by-products by sublimation in vacuo at 150°. A small fore-run (5 g.) and a residue of trimethyl citrate (3.5 g.) were obtained from the first distillation. Distillation of nearly pure dimethyl β-ketoglutarate (100 g.) (n\textsubscript{D}^2 1.4466) afforded two fractions:

<table>
<thead>
<tr>
<th>Fraction</th>
<th>B.P.</th>
<th>Wt. After distillation</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>77–77.7°/0.65–0.70 mm. 50 g.</td>
<td>1.4539</td>
</tr>
<tr>
<td>2</td>
<td>77–78°/0.65–0.7 mm. 40 g.</td>
<td>1.4538</td>
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</table>

After a week Fraction 1 had n\textsubscript{D}^2 1.4466.

When 31% fuming sulfuric acid (265 g.) was substituted in the foregoing procedure, the yield was 10% lower. At 0° the reaction between anhydrous citric acid and fuming sulfuric acid is slow even after half of the citric acid has been added. At the height of the reaction the foaming mixture fills a 2-L flask. The evolution of carbon monoxide is not complete even after 24 hr. The amount of fuming sulfuric acid employed is that calculated to convert all the water theoretically formed to sulfuric acid.

β-Ketoglutarate acid itself is perhaps obtainable in better yield than reported. The procedure in Organic Syntheses[p] prescribes U.S.P. citric acid, which is a monohydrate,[25] but when 25 g. of 2-carbomethoxytropinone (265 g.) was substituted in the foregoing procedure, the yield was 10% lower. At 0° the reaction between anhydrous citric acid and fuming sulfuric acid is slow even after half of the citric acid has been added. At the height of the reaction the foaming mixture fills a 2-L flask. The evolution of carbon monoxide is not complete even after 24 hr. The amount of fuming sulfuric acid employed is that calculated to convert all the water theoretically formed to sulfuric acid.

β-Ketoglutaric acid is its efferensce ('Merck Index', 6th Ed., p. 262), loses its moisture by exposure to air in dry weather, more readily by heating in vacuo at 60°.

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(27) The refractive index of the freshly distilled ester changed much more rapidly between the prisms of the refractometer than in the container. That of the equilibrated ester does not change between the prisms.


the yield reported there (85–90%) is calculated on the assumption that the anhydrous acid was used.

Under similar conditions dimethyl citrate and fuming sulfuric acid gave dimethyl β-ketoglutarate directly in about 10% yield.

Monomethyl β-ketoglutarate, diastatopium salt. A solution of potassium hydroxide (33.6 g, 0.90 mole) in absolute methanol (150 ml) was added dropwise at 0° during 35 min, to a mixture of dimethyl β-ketoglutarate (45.5 ml, 0.390 mole) and methanol (10 ml). When about one fifth of the alkali had been added a granular precipitate began to separate, and a yellow color appeared when the addition was about half complete.1 The mixture was kept 3 hours at room temperature during which period it became thicker. After storing overnight in the refrigerator, the salt was collected and washed with cold methanol (15 ml); 56.5 g.


Another experiment differing only in that the alkali was added at room temperature during 1 hr. afforded the same yield of salt of the same potassium content. Kept in a closed jar the salt slowly turned orange and after about a year contained about half complete. The mixture was kept overnight in the refrigerator, the salt was collected and washed with cold methanol (15 ml); 56.5 g.

Hyponitrous acid, which is known to result from the reaction of nitrous acid and hydroxylamine, slowly decomposes after standing overnight; and allowed to warm slowly.

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The base generated as described above melted as low as 58–88° and as high as 88–91° and was obtained in over-all yields of 69–79%.

Anal. Caled. for C$_6$H$_5$N$_2$O$_5$: C, 54.54; H, 6.87. Found: C, 54.29; H, 6.88.

In the first experiments, methylamine hydrochloride was always next neutralized by adding potassium bichromate. The yield of 2,4-dicarbomethoxytropinone in these experiments was comparatively low owing to the formation of large quantities of brown, polymeric by-products. By using lower temperatures and greater dilutions in the experiments with free methylamine the tendency to by-product formation was somewhat reduced; but the isolation became correspondingly more laborious, and in alkaline solution at any dilution some ester appeared always to be lost by hydrolysis. In the foregoing procedure, neutralization of only 10% of the methylamine hydrochloride with potassium hydroxide lowered the yield about 10%.

Properties of 2,4-dicarbomethoxytropinone. Anhydrous 2,4-dicarbomethoxytropinone was obtained only as an oil which was, at least moderately soluble in all common solvents, polar and non-polar. Isolated as described above the hemihydrate has usually a tan coloration, is relatively high melting, seems to be largely amorphous, and is partially (but not completely) liquefied by storing in vacuo over potassium hydroxide. Crystallized by dissolving in the minimum quantity of warm acetone, adding about 10% of water, seedling, and storing in the cold, the anhydrous oil afforded a white product melting at 82.5–84° and giving some extinction under the polarizing microscope.

Anal. Caled. for C$_6$H$_5$N$_2$O$_5$·CH$_2$O: C, 54.54; H, 6.87; CH$_2$O, 23.5. Found: C, 54.50; H, 6.76; CH$_2$O, 23.2.

A solution composed of equal parts of the hemihydrate and methanol was mixed with the theoretical amount of powdered oxalic acid dihydrate. On cooling the solution and scratching the binoxalate crystallized out: aggregates of minute, colorless prisms melting at 143–145° or at 148° and remaining colorless. The higher-melting binoxalate described above could not be thus obtained.

Anal. Caled. for C$_6$H$_5$N$_2$O$_5$: C, 48.69; H, 5.55; CH$_2$O, 17.96. Found: C, 48.43; H, 5.58; CH$_2$O, 17.54.

The nitrate was prepared from 3N nitric acid at 0° and purified from methanol-ether and from acetone: minute, stout prisms, m.p. 146–148°.

Anal. Caled. for C$_6$H$_5$N$_2$O$_5$·HNO$_3$: C, 45.28; H, 5.70. Found: C, 45.34; H, 5.66.

The picrate was prepared in aqueous acetone and purified from acetone: needles, m.p. 167–167.5°.

Anal. Caled. for C$_6$H$_5$N$_2$O$_5$·1/2H$_2$O: C, 43.82; H, 4.29. Found: C, 43.84; H, 4.26.

Racemic 2-carbamethoxytropinone (1). (a) From 2,4-dicar-
bomethoxypipone. Finely divided 2,4-dicarbomethoxytropinone hemihydrate (21.1 g., 0.0800 mole) was dissolved at room temperature with stirring in 50 ml. of aqueous sodium hydroxide (5.0 g.) and saturated aqueous sodium sulfate (25 ml.) to 100 ml. of aqueous solution. During the stirring (5 hr.) the light orange mixture became turbid. After keeping 48 hr. at room temperature, this mixture, which had become a yellowish white semi-solid, was suspended in water (50 ml.) and 6 N aqueous sulfuric acid (27.5 ml.) added cautiously (effervescence) to pH 4.0. The mixture was made basic with potassium bicarbonate (12 g.) and extracted with chloroform (5 × 50 ml.). After removing about 75% of the solvent from the dried (Na₂SO₄) extracts on the steam bath, the solution was concentrated in vacuo to a yellow oil which slowly solidified when seeded: ~16 g. of crude product.

This was purified by dissolving it in hot methyl acetate (20 ml.), adding to the cold solution water (4 ml.) and acetone (4 ml.), and keeping several hours at 0 °C. The yellowish product was collected and washed with cold methyl acetate: 10.3 g., m.p. 97-101 °C. From the mother liquors additional material was recovered. By evaporative distillation about 100/1 mm. a solid, partly yellow and partly white, was obtained (64% m.p. 102.5-105.8 °C) of anhydride base. No tropinone was isolated unless excess base was used in the saponification.

One part of diester dissolved in two parts of acetone and the stoichiometric amount of 4 N aqueous sodium hydroxide gave a lower yield of the keto ester.

(b) From the dipotassium salt of dimethyl β-ketoglutarate. The potassium salt and succinylidihyde, prepared as described above, were combined with methylamine approximately according to the directions of Willstätter. Based either on succinylidihyde or on the dipotassium salt, the yield of 2-carbomethoxytropinone was 45%.

(c) From β-ketoglutaric anhydride. β-Ketoglutaric acid (40 g.) was suspended in a mixture of glacial acetic acid (50 ml.) and ace
tone (43 g.) at ca. 0 °C and stirred 1 hr. at room temperature. It was added to a solution of methylamine hydrochloride (10.0 g., 0.148 mole) and sodium hydroxide (4.0 g., 0.100 mole) in water (850 ml.) and aqueous succinylidihyde (125 ml. of ca. 0.8 N) stirred in. The mixture warmed almost imperceptibly, turned slowly yellow, and evolved carbon dioxide slowly. After keeping 24 hr. at room temperature the yellow solution was brought to pH 4.0 with 6 N mineral acid (effervescence), washed with chloroform (35 ml.) to remove neutral and colored by-products, basified with sodium hydroxide (20 ml. of 4 N) and potassium bicarbonate (4 g.), and extracted with chloroform (9 × 100 ml.). Recovered as above described racemic 2-carbomethoxytropinone was obtained as a yellowish brown oil which, when seeded, slowly crystallized as yellowish brown warts: 16.9 g. (86%), m.p. 92-93 °C. This material was recrystallized from acetone-water as described above; 12.1 g., m.p. 96-98.5 °C, of granular, pale yellow product. By sublimation in vacuo this and the material from the mother liquors were freed of water and small amounts of resinous impurities: 11.6 g. (59%), m.p. 93-100 °C.

When the reactants were combined near 0 °C and the mixture kept in the refrigerator 24 hr., the yield was somewhat lower: 10.3 g. (52%), m.p. 99.5-104.4 °C. When no sodium hydroxide was used to generate (f)ethylenimine, the yield of the keto ester was even smaller, and a proportionately greater quantity of resinous by-products was obtained.

Properties of racemic 2-carbomethoxytropinone. The analytically pure base was obtained by mixing the picrate (6.1 g., m.p. 167-168 °C), described below, with potassium car
The prisms melted about 98° and, when partially dehydrated, again at 145° (bubbling, but little or no discoloration). They are not completely dehydrated by heating in vacuo first at 57° and then 12 hr. at 80°.

**Anal.** Calcd. for C_{10}H_{15}NO_{3}: C, 60.98; H, 7.73. Found: C, 60.98; H, 7.73.

The hydrated form was obtained by mixing with a slight excess of distilled water and drying in vacuo over anhydrous sodium sulfate. **Anal.** Calcd. for C_{10}H_{15}NO_{3} \cdot 2H_{2}O: C, 51.49; H, 8.21. Found: C, 51.16, 51.16; H, 7.85, 8.22.

To a solution of the hydrate (0.60 g.) in methanol (-1 ml.) was added picric acid (0.64 g.) dissolved in methanol (1 ml.). The precipitate separated slowly from the supersaturated solution as balls of prisms: m.p. 176-177° (dec.). **Anal.** Calcd. for C_{10}H_{15}NO_{3} \cdot C_{4}H_{6}O_{6}: C, 48.41; H, 6.08. Found: C, 48.29; H, 6.08. CH_{3}O, 8.93. Found: C, 48.41; H, 6.10; CH_{3}O, 8.93.

Evidence of the transitory existence of a more dextrorotatory L-bitartrate was obtained.

The d-base was obtained by mixing the salt with a slight excess of potassium bicarbonate, extracting with chloroform, removing the solvent, and subliming the residue: colorless, minute prisms, m.p. 108.5-109.5°, which electrically readily; [α]_{D}^{20} +18.3° (c, 1, methanol).

The bitartrate prepared in water from stoichiometric amounts of the d-base and D-tartaric acid was obtained as colorless, rather stout prisms by evaporation at room temperature. These were converted to the anhydrous salt by dissolving in methanol and removing the solvent at room temperature. This form was recrystallized from absolute methanol in which it is noticeably less soluble than the hydrate: rosettes of prisms (which were dried over CaCl_{2}, m.p. 145-146° (dec.), [α]_{D}^{20} -7.0° (c, 2.5, water).

**Anal.** Calcd. for C_{10}H_{15}NO_{3} \cdot C_{4}H_{6}O_{6}: C, 48.41; H, 6.08. Found: C, 48.32; H, 6.08.

The hydrated form was obtained by mixing with a slight excess of distilled water and drying in vacuo over anhydrous sodium sulfate. **Anal.** Calcd. for C_{10}H_{15}NO_{3} \cdot 2H_{2}O: C, 51.49; H, 8.21. Found: C, 51.16, 51.16; H, 7.85, 8.22.

To a solution of the hydrate (0.60 g.) in methanol (-1 ml.) was added picric acid (0.64 g.) dissolved in methanol (1 ml.). The precipitate of the L-base separated suddenly from the supersaturated solution as balls of prisms: m.p. 176-177° (bubbling). These were recrystallized from methanol: minute, slender prisms, m.p. 170-176.5° (bubbling). The sample was dried to constant weight at 125° in vacuo alto for analysis (weight loss: 1.49%).

**Anal.** Calcd. for C_{10}H_{15}NO_{3} \cdot C_{4}H_{6}O_{6}: C, 48.41; H, 6.08. Found: C, 48.32; H, 6.08.

Recrystallized to constant melting point from acetone the salt was obtained as a white slender prisms: m.p. 159.5° (elev.). **Anal.** Calcd. for C_{10}H_{15}NO_{3} \cdot C_{4}H_{6}O_{6}: C, 48.32; H, 6.08. Found: C, 48.29; H, 6.08.

The d-base was obtained by mixing the salt with a slight excess of potassium bicarbonate, extracting with chloroform, removing the solvent, and subliming the residue: colorless, minute prisms, m.p. 108.5-109.5°, which electrically readily; [α]_{D}^{20} +18.3° (c, 1, methanol).

The bitartrate prepared in water from stoichiometric amounts of the d-base and D-tartaric acid was obtained as colorless, rather stout prisms by evaporation at room temperature. These were converted to the anhydrous salt by dissolving in methanol and removing the solvent at room temperature. This form was recrystallized from absolute methanol in which it is noticeably less soluble than the hydrate: rosettes of prisms (which were dried over CaCl_{2}, m.p. 145-146° (dec.), [α]_{D}^{20} -7.0° (c, 2.5, water).

**Anal.** Calcd. for C_{10}H_{15}NO_{3} \cdot C_{4}H_{6}O_{6}: C, 48.41; H, 6.08. Found: C, 48.32; H, 6.08.

The hydrated form was obtained by mixing with a slight excess of distilled water and drying in vacuo over anhydrous sodium sulfate. **Anal.** Calcd. for C_{10}H_{15}NO_{3} \cdot 2H_{2}O: C, 51.49; H, 8.21. Found: C, 51.16, 51.16; H, 7.85, 8.22.

To a solution of the hydrate (0.60 g.) in methanol (-1 ml.) was added picric acid (0.64 g.) dissolved in methanol (1 ml.). The precipitate of the L-base separated suddenly from the supersaturated solution as balls of prisms: m.p. 176-177° (bubbling). These were recrystallized from methanol: minute, slender prisms, m.p. 170-176.5° (bubbling). The sample was dried to constant weight at 125° in vacuo alto for analysis (weight loss: 1.49%).

**Anal.** Calcd. for C_{10}H_{15}NO_{3} \cdot C_{4}H_{6}O_{6}: C, 48.41; H, 6.08. Found: C, 48.32; H, 6.08.

Recrystallized to constant melting point from acetone this form gives another modification melting at 174° (bubbling) which seems, however, to be indistinguishable from the first in crystalline form. It was similarly dried for analysis.

**Anal.** Calcd. for C_{10}H_{15}NO_{3} \cdot C_{4}H_{6}O_{6}: C, 48.41; H, 6.08. Found: C, 44.95; H, 4.46.

The binoxalate was prepared in methanol and crystallized therefrom by adding ether; m.p. 142-143°.

**Dehydrogenation experiments.** Efforts to dehydrogenate ecodegone, ecodegone methyl ester, and pseudoecgone methyl ester in alcoholic solution with freshly prepared Raney nickel did not succeed. Silver carbonate in bolling benzene had no effect on either of the foregoing esters. No 2-carboxymethoxystrophi onone was obtained from pseudoecgone methyl ester by the action of N-bromosuccinimide in chloro-

form, by the action of N-bromosuccinimide, or by the Oppenauer oxidation. The irradiation of a fused mixture of pseudoephedrine methyl ester and benzophenone containing a small amount of glacial acetic acid with a G.E. Sunlamp produced no 2-carbethoxycryptopine as indicated by a negative ferric chloride test.

**d-(2-Carbethoxytropinone) from pseudoephedrine methyl ester.** Kiliani’s chromic acid solution (4.0 ml.) was added dropwise during 1 hr. to a stirred solution of pseudoephedrine methyl ester (1.0 g.) dissolved in Fisher Reagent acetone (250 ml.). The first third of the reagent produced an orange turbidity. The remainder caused a color change to greenish orange and the separation of a granular, greenish deposit. Dropwise during 1 hr. to a stirred solution of pseudoephedrine methyl ester (250 ml.). The first third of the reagent produced an orange and the separation of a granular, greenish deposit. The residue recovered in the customary manner: -0.6 g. of d-(a-carboxymethoxytropinone) was obtained.

**Extraction** of the residue with water (25 ml.) was warmed and agitated until the mixture became homogeneous. It was diluted with glacial acetic acid (200 ml.), 2.5-diethoxytetrahydrofuran (16 g.) as described under "Tropinone," was distilled to 125 ml., mixed with methylamine hydrochloride (6.75 g.), then with potassium bicarbonate (10.0 g.), and finally with methyl acetate (10.7 ml.) in methanol (550 ml.). The pale green solution had become brown within a few hours. During the next 2 weeks the solution did not become noticeably darker. The product was filtered and concentrated in vacuo to a mixture of water and oil which partially crystallized on keeping. Purified from methanol it was obtained as minute, stout prisms: 5.9 g. (20%), m.p. 119-124°.

**Spectral measurements.** In chloroform solution the optical rotation of the sublimed material exhibited pronounced absorption at 5.76 μ, 5.85 μ, 6.02 μ, and 6.45 μ.

**Acknowledgment.** The writer is indebted to the Carbide and Carbon Chemicals Company, the

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1-Mesitoyl-2-methoxynaphthalene (I) reacts with the dimagnesium derivatives (II) of 1,4-dibromobutane, 1,5-dibromopentane, and 1,6-dibromohexane to yield products that could be derived from intermediate keto Grignard reagents (III). With 1,4-butanedimagnesium dibromide, for example, the principal product is 2-(7-butenyl)naphthyl-1-mesitylcarbinol (V, n = 2). The amount of reduction product decreases progressively as the chain of the Grignard reagent is lengthened. Similarly, duryl-2-methoxyphenyl ketone (X) and the Grignard reagent from 1,4-dibromobutane gave 2-(7-butenylphenyl)duryl-carbinol (XII).

The condensation of esters with certain aliphatic bifunctional Grignard reagents to give cyclic carbinols appears to involve the formation of keto Grignard reagents as transient intermediates. The object of the present study was to determine whether such a keto Grignard reagent could be produced by the action of a dibromomagnesium compound on a hindered ω-methoxyaryl ketone, a vinylog of an indane.

1-Mesitoyl-2-methoxynaphthalene (I) has been found to react with the Grignard reagent from 1,4-dibromobutane (II, n = 2) to give the olefinic carbinol V (n = 2) in a yield of 65%. This unexpected product was formed presumably by way of the keto Grignard reagent III (n = 2), which may undergo intramolecular reduction by way of a transition state resembling the quasi-cyclic system IV (n = 2).

Oxidation with dichromate in glacial acetic acid, by preferential attack of the carbinol function, produced the olefinic ketone VI (n = 2), which was hydrogenated catalytically to give 2-n-butyl-1-mesitoylnaphthalene (VII, n = 2).

The terminal position of the double bond in the side chain of the carbinol was established by ozonization. In addition to formaldehyde, a larger frag-