Preparation and Baeyer–Villiger Reaction of Certain 2-Carbalkoxycyclopropyl Methyl Ketones

JOSEPH G. CANNON ˣ and JOHN E. GARST

Abstract □ Treatment of mixed anhydrides derived from *cis*- and *trans*-2-carbobenzyloxycyclopropanecarboxylic acids and ethyl chloroformate with ethoxymagnesio di-*tert*-butyl malonate and subsequent treatment of the resulting adducts with *p*-toluenesulfonic acid afforded *cis*- and *trans*-benzyl 2-acetylcyclopropanecarboxylates in good to excellent yields, with retention of the original stereochemistry of the systems. These methyl ketones and an open chain congener, benzyl levulinate, were inert toward *m*-chloroperbenzoic acid. The *cis*-isomer and benzyl levulinate underwent normal Baeyer–Villiger reactions mediated by trifluoroperacetic acid, forming moderate yields of the acetate ester insertion products.

Keyphrases □ 2-Acetoxycyclopropanecarboxylic acid esters—synthesis from 2-carbalkoxycyclopropyl methyl ketones, Baeyer–Villiger reaction, retention of stereochemistry □ 2-Carbalkoxycyclopropyl methyl ketones—Baeyer–Villiger reaction, synthesis of stereospecific 2-acetoxycyclopropanecarboxylic acid esters

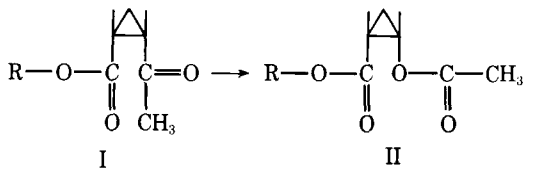
As a part of a synthetic program leading to partially rigid analogs of acetylcholine, a preparative route to *cis*-2-acetoxycyclopropanecarboxylic esters (II) was required. It was proposed that these systems should be attainable *via* Baeyer–Villiger oxidation of an appropriate methyl ketone (I) (Scheme I).

DISCUSSION

It was speculated that the malonic ester adduct (III) could be converted into I by decarboxylation of the malonic ester moiety and esterification of the ring carboxyl group. Treatment of *cis*-cyclopropane-1,2-dicarboxylic anhydride with sodio di-*tert*-butyl malonate gave a 3% yield of the expected product (III) (R = *tert*-butyl) and 33% of a neutral solid (IV), whose structure was assigned on the basis of spectral and analytical data and of literature precedent (1). Attempts to effect acid-catalyzed conversion of IV into a methyl ketone failed.

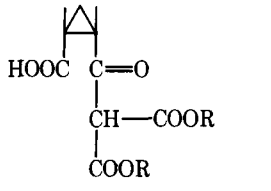
Treatment of *cis*-2-carbomethoxycyclopropanecarbonyl chloride with methoxymagnesio dimethyl malonate (V) gave a 24% yield of the predicted product (VI), whose NMR spectrum demonstrated broad resonance signals at δ1.10–2.80. These signals were typical of other *cis*-1,2-dicarbonyl cyclopropane systems encountered in the present work.

Repeated attempts to prepare *cis*-2-carbobenzyloxycyclopropanecarbonyl chloride led only to elimination of benzyl chloride and isolation of *cis*-cyclopropane-1,2-dicarboxylic anhydride. Reaction of the mixed anhydride (VII) with ethoxymagnesio di-*tert*-butyl malonate and treatment of the malonate adduct (VIII) with *p*-toluenesulfonic acid, according to a method of Fonken and Johnson (2), permitted good overall yields of the *cis*-methyl ketone (IX) (Scheme II). A similar reaction sequence on *trans*-2-carbobenzyloxycyclopropanecarbonyl chloride gave a 76% overall yield of the *trans*-isomer (X). Retention of the *cis*-geometry of IX was verified by comparison of its NMR spectrum with that of X. A reaction between the mixed anhydride (VII) and methylmagnesium iodide resulted in a mixture of the *cis*- and *trans*-isomers (IX and X).

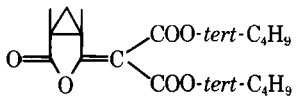


I II

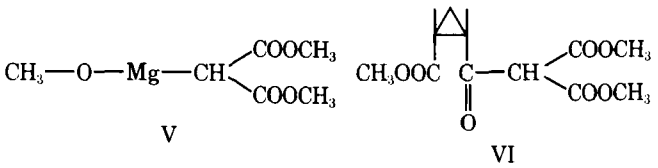
Scheme I



III



IV



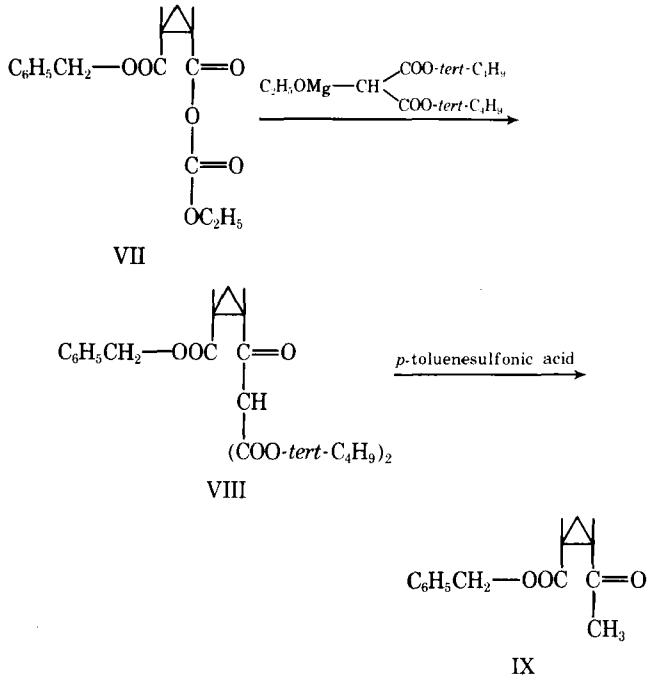
V VI

Sauers and Ubersax (3) reported a 20% yield of a mixture of Baeyer–Villiger products of methylcyclopropyl ketone, using *m*-chloroperbenzoic acid or trifluoroperacetic acid. The remaining 80% of the starting ketone was recovered unchanged. In the present work, *cis*-benzyl 2-acetylcyclopropanecarboxylate was unchanged (according to NMR analysis) after 10 days of stirring with *m*-chloroperbenzoic acid. Treatment of benzyl levulinate (XI), an open chain congener of the cyclopropane methyl ketone systems, with *m*-chloroperbenzoic acid failed to afford detectable reaction products after 10 days of stirring at room temperature. Baeyer–Villiger oxidation of benzyl levulinate into benzyl 3-acetoxypropionate (XIII) was achieved (in 65% yield) with trifluoroperacetic acid in an oxidant–ketone ratio of 4.4:1. This reagent, in a ratio of 8.8:1, converted *cis*-benzyl 2-acetylcyclopropanecarboxylate into the acetoxy insertion product (XII). When less oxidizing agent was employed, large amounts of unchanged starting ketone could be recovered.

EXPERIMENTAL[1]

Di-*tert*-butyl 2-Keto-3-oxa-[3.1.0]-bicyclohexyl-4-idene Malonate (IV)—Di-*tert*-butyl malonate (3) (65.1 g, 0.3 mole) in 200 ml of anhydrous benzene was added dropwise with stirring to 200 ml of anhydrous benzene containing 14.4 g (0.3 mole) of 50% sodium hydride in mineral oil, which had been washed with three 50-ml portions of hexane. The resulting mixture was refluxed for 2 hr, then 33.6 g (0.3 mole) of *cis*-cyclopropane-1,2-dicarboxylic anhydride (4) in 100 ml of anhydrous benzene was added dropwise, and this mixture was refluxed overnight. The solvent was removed under reduced pressure, and the solid residue was dissolved in 300 ml of water. This solution was extracted with ether and the extract was dried over magnesium sulfate. The water solution was reserved as Solution A and was utilized in the isolation of III. Evaporation of the ethereal solution gave a solid, which was recrystallized from hexane to yield 30.9 g (33%) of product, mp 117–119°; IR (potassium bromide): 3110 (cyclopropane CH), 2980 (*tert*-

[1] Boiling points are uncorrected. Melting points were determined in open glass capillaries, using a Thomas-Hoover Uni-Melt apparatus, and are corrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by the Microanalytical Service, College of Pharmacy, University of Iowa. NMR spectra were recorded on a Varian Associates T-60 instrument relative to an internal standard of tetramethylsilane. IR spectra were obtained with a Beckman IR-10 instrument.



Scheme II

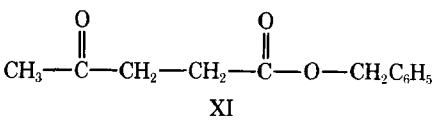
C_4H_9), 1814 (lactone C=O), 1720–1708 (ester C=O), and 1660 (C=C) cm^{-1}; NMR (deuterochloroform): δ 1.50 (s, 18H, *tert*-C_4H_9), 1.20–1.80 (m, 2H, ring CH_2), 2.10–2.60 (m, 1H, CHC=O), and 3.48–3.84 (m, 1H, CHC=C).

Anal.—Calc. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.14. Found: C, 61.60; H, 7.14.

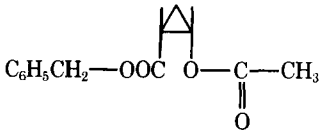
***cis* - 2 - [Di(carbo-*tert*-butoxy)acetyl]cyclopropanecarboxylic Acid (III)**—Acidification of Solution A from the preparation of IV with 6 *N* hydrochloric acid gave a solid, which was recrystallized from ether to afford 3 g (3%) of product, mp 129–130.5°; IR (mineral oil): 3350–2600 (acid OH), 1710 (acid C=O), 1734, and 1750 (ester C=O) cm^{-1}; NMR (deuterochloroform): δ 1.50 (s, 18 H, *tert*-C_4H_9), 1.15–1.60 (m, 2H, ring CH_2), 2.00–2.65 (m, 2H, ring CH), 4.39 [s, 1H, $CH(CO_2R)_2$], and 9.13 (broad s, 1H, CO_2H).

Anal.—Calc. for $C_{16}H_{24}O_7$: C, 58.55; H, 7.35. Found: C, 58.51; H, 7.44.

***cis*-Methyl 2-[Di(carbomethoxy)acetyl]cyclopropanecarboxylate (VI)**—Carbon tetrachloride (1 ml) was added to a mixture of 2.4 g (0.1 g-atom) of magnesium turnings, 42 ml of anhydrous methanol, and 13.2 g (0.103 mole) of dimethyl malonate. Within 3–5 min, the evolution of gas became vigorous and was moderated by external cooling. After the magnesium had dissolved, excess methanol was azeotroped with anhydrous benzene under reduced pressure. Fresh anhydrous benzene (100 ml) was added, and this solution was added dropwise with stirring to 15.9 g (0.098 mole) of freshly distilled *cis*-2-carbomethoxycyclopropanecarbonyl chloride (5); stirring was continued for 1 hr. After standing for 12 hr at room temperature, 200 ml of ether was added and the resulting solution was poured into 100 ml of 6 *N* hydrochloric acid. The organic layer was washed with water until the washings were neutral to litmus and was dried over magnesium sulfate. Evaporation of the volatiles left an oil, which was distilled at 120–124° (0.05 mm) to yield 6.0 g (24%) of product; IR (film): 1740



XI



XII

(ester C=O) and 1650 (C=C) cm^{-1}; NMR (deuterochloroform): δ 1.10–2.80 (m, 4H, ring H), 3.67 (s, 3H, CO_2CH_3), 3.80, 3.83 (2 s, 6H, malonate CH_3), 4.60 [s, 0.5H, $CH(CO_2R)_2$], and 13.71 (s, 0.5H, enol OH).

Anal.—Calc. for $C_{11}H_{14}O_5$: C, 51.16; H, 5.46. Found: C, 51.15; H, 5.16.

***cis*-Benzyl 2-Acetylcyclopropanecarboxylate (IX)**—To a stirred, cooled (0°) solution of 11 g (0.05 mole) of *cis*-2-carbobenzyloxycyclopropanecarboxylic acid (5) in 200 ml of anhydrous ether was added dropwise 5.1 g (0.05 mole) of triethylamine. After stirring for 10 min, 5.4 g (0.05 mole) of ethyl chloroformate was added dropwise over 5 min; stirring was continued at 0° for 0.5 hr. The reaction mixture was filtered and the filtrate was reserved as Solution A. Carbon tetrachloride (1 ml) was added to 13 g (0.06 mole) of di-*tert*-butyl malonate, 1.2 g (0.05 g-atom) of magnesium turnings, and 4 g (0.087 mole) of anhydrous ethanol. Evolution of gas began immediately, and 50 ml of anhydrous dimethoxyethane was added within 3–5 min. The temperature was maintained at 30–40°, and most of the magnesium had dissolved after 1 hr.

This reaction mixture was cooled to 0° and was added dropwise, with rapid stirring, to cooled (0°) Solution A. After stirring for 1 hr, the reaction mixture was allowed to come to room temperature overnight. It was then poured into 200 ml of cold (0°) 3 *N* hydrochloric acid, and this solution was extracted with three 100-ml portions of ether. The combined organic extracts were washed with water and extracted with 50 ml of 10% potassium carbonate solution and with three 100-ml portions of water. The organic phase was acidified by washing with 25 ml of 6 *N* hydrochloric acid and dried over magnesium sulfate, and the ether was removed under reduced pressure to afford 18.5 g of an oil. This oil was refluxed with 1.5 g of *p*-toluenesulfonic acid monohydrate in 100 ml of toluene for 5 hr; the solution was cooled and then extracted with 10% potassium carbonate solution until the washings were basic. The organic layer was washed with 20 ml of 6 *N* hydrochloric acid and then with several portions of water. After drying over magnesium sulfate, the volatiles were removed and the residue was distilled at 104–108° (0.05 mm) to afford 6.3 g (58%) of IX; IR (film): 1730 with a shoulder at 1700 (ester and ketone C=O) cm^{-1}; NMR (deuterochloroform): δ 0.92–1.40, 1.50–1.90, 2.00–2.35 (m, 4H, ring H), 2.20 (s, 3H, CH_3), 5.10 (s, 2H, CH_2Ar), and 7.34 (s, 5H, ArH).

Anal.—Calc. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.72; H, 6.59.

***trans*-Benzyl 2-Acetylcyclopropanecarboxylate (X)**—Ethoxymagnesio di-*tert*-butyl malonate was prepared in the same manner as IX from 1 ml of carbon tetrachloride, 6.15 g (0.03 mole) of di-*tert*-butyl malonate, 0.7 g (0.029 g-atom) of magnesium turnings, 1.9 g (0.042 mole) of anhydrous ethanol, and 50 ml of anhydrous dimethoxyethane. The cooled (0°) solution was added dropwise over 10 min to 6.8 g (0.0285 mole) of *trans*-2-carbobenzyloxycyclopropanecarbonyl chloride (5) in 200 ml of anhydrous benzene. The reaction mixture was refluxed for 5 hr and was worked up as described for IX, yielding 4.7 g (76%), bp 99–102° (0.05 mm); IR (film): 1729 (ester C=O) and 1705 (ketone C=O) cm^{-1}; NMR (deuterochloroform): δ 1.25–1.55 (m, 2H, ring CH_2), 2.05–2.65 (m, 2H, 2CHCO), 2.27 (s, 3H, CH_3), 5.16 (s, 2H, $CH_2C_6H_5$), and 7.36 (s, 5H, ArH).

Anal.—Calc. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.72; H, 6.63.

Benzyl 3-Acetoxypropionate (XIII)—Ninety percent hydrogen peroxide (11.4 g, 0.44 mole) was added dropwise over 0.5 hr to a stirred, cooled (0°) solution of 92 g (0.44 mole) of trifluoroacetic anhydride in 100 ml of methylene chloride. After cooling at 0° for 0.25 hr, the trifluoroperacetic acid solution was added dropwise to a rapidly stirred mixture of 120 g of anhydrous disodium phosphate, 200 ml of methylene chloride, and 20.6 g (0.1 mole) of benzyl levulinate (6). The resulting mixture refluxed within 0.5 hr and continued spontaneously for 2 hr. Refluxing was maintained for 4 hr total. The methylene chloride solution was filtered, and the solid on the filter was washed with two 300-ml portions of methylene chloride and then was refluxed for 10 min with an additional 300-ml portion of methylene chloride. The combined organic extracts were washed successively with 10% potassium carbonate solution, water, 6 *N* hydrochloric acid, and water and were dried over magnesium sulfate. The solvent was removed, and the residue was distilled through a 10-cm Vigreux column, bp 87–90° (0.04 mm). The yield was 10.2 g (63%); IR (film): 1741 (ester C=O) cm^{-1};

NMR (deuterochloroform): δ 2.00 (s, 3H, CH_3), 2.67 (t, 2H, CH_2CO_2R), 4.34 (t, 2H, CH_2OCOCH_3), 5.14 (s, 2H, $CH_2C_6H_5$), and 7.32 (s, 5H, ArH).

Anal.—Calc. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.34. Found: C, 65.01; H, 6.27.

***cis*-Benzyl 2-Acetoxycyclopropanecarboxylate (XII)**—A procedure similar to that described for XIII was utilized with 10.9 g (0.05 mole) of IX and 57.2 g (0.44 mole) of trifluoroperacetic acid. The 3.3 g of crude oily product was treated with 4.8 g of Girard's reagent P[2] and 3 ml of acetic acid in 40 ml of refluxing methanol for 4 hr. Ice water (50 ml) was added to the hot solution, and it was brought to neutrality with solid potassium carbonate. This solution was extracted with methylene chloride, and the extract was washed with water and dried over magnesium sulfate. Removal of the solvent and distillation of the residual liquid at 113° (0.035 mm) gave 2.5 g (25%) of product; IR (film): 1730 (ester C=O) cm^{-1}; NMR (deuterochloroform): δ 1.08–2.23 (m, 3H, ring H), 1.93 (s, 3H, CH_3), 4.00–4.44 (m, 1H, $CHOCOCH_3$), 5.16 (s, 2H, $CH_2C_6H_5$), and 7.38 (s, 5H, ArH).

Anal.—Calc. for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.49; H, 6.18.

[2] Eastman.

REFERENCES

(1) S. Eskola, T. Tirvonen, and K. Kiianlinna, *Suom. Kemistlekti*, **338**, 80(1960).

(2) G. S. Fonken and W. S. Johnson, *J. Amer. Chem. Soc.*, **74**, 831(1952).

(3) R. R. Sauers and R. W. Ubersax, *J. Org. Chem.*, **30**, 3939(1965).

(4) L. L. McCoy, *J. Amer. Chem. Soc.*, **80**, 6568(1958).

(5) J. G. Cannon and J. E. Garst, *J. Org. Chem.*, **40**, 182(1975).

(6) P. P. T. Shah, H. H. Lei, and H. M. Fang, *J. Amer. Chem. Soc.*, **55**, 4727(1933).

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Synthesis and Biological Evaluation of 2-(9-Acridinyl)ethyl-*N*-substituted Carbamates and Their Hydrochlorides and 10-*N*-Oxides

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Abstract □ The syntheses of 2-(9-acridinyl)ethyl-*N*-substituted carbamates and their hydrochlorides and 10-*N*-oxides are reported along with biological results in the areas of antineoplastic, antimalarial, and CNS activity screening. The compounds showed negative biological activity in the areas tested.

Keyphrases □ 2-(9-Acridinyl)ethyl-*N*-substituted carbamates, hydrochlorides, and 10-*N*-oxides—synthesis, pharmacological activity □ Antineoplastic activity—synthesis and screening of 2-(9-acridinyl)ethyl-*N*-substituted carbamates, hydrochlorides, and 10-*N*-oxides

Acridine derivatives have been tested extensively for potential medicinal activity. Antibacterial (1, 2), antimalarial (3), anthelmintic (4), analeptic (5), and antineoplastic (6–10) activities have been reported for many substituted acridines. The synthesis of new acridine derivatives containing urea, thiourea, thiocarbamate, and carbamate groupings has been reported from this laboratory (11, 12). While possessing little or no anticancer activity, a general pharmacological screen revealed activity in antibacterial, metabolic, parasitologic, and GI screening procedures for some derivatives.

In a continuation of a study into the synthesis and potential biological activity of new acridine compounds, this paper reports the synthesis and antineoplastic screening data for 2-(9-acridinyl)ethyl-*N*-substituted carbamates and their hydrochlorides and 10-*N*-oxides. In addition, biological results for some compounds in antimalarial and central nervous system (CNS) activity screening procedures are reported.

DISCUSSION

The incorporation of the carbamate and acridine moieties into one structure is of special interest, since each structure is singly present in compounds that have shown various degrees of antineoplastic activity (6–10, 13–15). The interaction of acridines with nucleic acids and inhibition of nucleic acid synthesis is well documented (16, 17). Acridines tend to accumulate selectively in tumor tissue (18, 19) showing inhibition of tumor growth, reduction of rate of growth, and, in some cases, regression of tumor size. Nevertheless, no clinically useful agent has been found among the acridines tested, most of which have been substituted 9-aminoacridines. Structures containing carbamate esters also have been reported to have potent antitumor activity (13, 14). Ethyl carbamate itself has been used both for the production of tumors in experimental animals and for the treatment of chronic leukemia and multiple myeloma (15). Some evidence also indicates that carbamates are involved in alkylation of DNA (20).

The mechanism by which these new acridine carbamates were expected to exert their antineoplastic effect was by selective absorption in cancerous tissue followed by a two-pronged attack upon the nucleic acids of the cancer cells. The acridine ring would be expected to interact with the nucleic acid bases, thus holding the carbamate portion in close proximity to the bases to facilitate alkylation by the carbamate.