Anal. Calcd. for $C_{16}H_{19}F_3N_4O_8 \cdot H_2O$: C, 40.85; H, 4.50. Found: C, 41.44; H, 5.26.

1,1,1-Trifluoro-3-piperidinomethyl-2-hexanone hydrate (VII, R = *n*-propyl). Trifluoromethyl *n*-butyl ketone[16] (15.4 g., 0.1 mole) was treated with 8.5 g. (0.1 mole) of piperidine and 10 ml. of 37% formalin, yielding 23 g. (85%) of product. After recrystallization from aqueous methanol it melted at 82–84°.

Anal. Calcd. for $C_{12}H_{20}F_3NO \cdot H_2O$: C, 53.55; H, 8.24. Found: C, 54.09; H, 8.74.

The *picrate*, recrystallized from aqueous methanol, had m.p. 93–95°.

Anal. Calcd. for $C_{18}H_{23}F_3N_4O_8 \cdot H_2O$: C, 43.37; H, 5.06. Found: C, 43.81; H, 5.53.

N-(α-trifluoroacetyl-β-piperidinopropionyl)piperidine hydrate (VII, R = $CON(C_5H_{10})$). A solution of 5 g. (0.22 mole) of N-(γ,γ,γ-trifluoroacetoacetyl)piperidine V in 20 ml. of 95% ethanol was cooled to 10° and treated with 1.9 g. (0.22 mole) of piperidine and 2.2 g. (0.22 mole) of 30% formalin with cooling and shaking. There was obtained 6.8 g. (90%) of product which, after recrystallization from ether–petroleum ether (b.p. 30–60°), had m.p. 96–98°.

Anal. Calcd. for $C_{15}H_{23}F_3N_2O_2 \cdot H_2O$: C, 53.25; H, 7.45; neut. equiv., 338. Found: C, 53.35; H, 7.39; neut. equiv., 339.

The *picrate*, after washing with ether, had m.p. 92–93°.

Anal. Calcd. for $C_{21}H_{26}F_3N_5O_9 \cdot H_2O$: C, 44.44; H, 4.97; neut. equiv., 567. Found C, 44.41; H, 4.96; neut. equiv., 566.

An attempt to recrystallize the Mannich base from hot aqueous methanol caused its decomposition to VIII.

N-(α-trifluoroacetylacryloyl)piperidine hydrate (VIII). A solution of 5 g. (0.22 mole) of *N*-(γ,γ,γ-trifluoroacetoacetyl)piperidine V in 15 ml. of methanol, to which ten drops of 15% NaOH had been added, was cooled to 20° and treated with 3 g. (0.03 mole) of 30% formalin, added dropwise with vigorous shaking. After heating the mixture to 50° and shaking vigorously for 5 min., 5 ml. of water was added and the mixture was cooled, affording 4 g. (70%) of product which was recrystallized from aqueous methanol, m.p. 138.4–140.0°.

Anal. Calcd. for $C_{10}H_{12}F_3NO_2 \cdot H_2O$: C, 47.43; H, 5.57. Found: C, 48.05; H, 5.38.

1,1,1-Trifluoro-3-piperidinomethyl-2-butanol (IX). To a solution of 5 g. (0.023 mole) of 1,1,1-trifluoro-3-piperidinomethyl-2-butanone hydrate (compound VII, R = CH_3) in 100 ml. of ether was added in small portions 0.38 g. (0.01 mole) of sodium borohydride. Stirring was continued for 1.5 hr. Unreacted borohydride was removed by filtration and the filtrate was treated with a solution of 2 g. of sodium hydroxide in 50 ml. of water and the mixture was stirred vigorously for 1 hr. The water layer was separated and extracted with ether and the combined ether extracts were dried over magnesium sulfate. Upon distillation of the ether extracts 2.5 g. (50%) of a colorless oily liquid, b.p. 79–81° (4 mm.), was obtained.

p-Nitrobenzoate hydrochloride. Recrystallized from a chloroform–petroleum ether solution, m.p. 206–208° (corr.).

Anal. Calcd. for $C_{17}H_{22}O_4F_3N_2Cl$: C, 49.69%; H, 5.39%. Found: C, 49.51%; H, 6.18%.

1,1,1-Trifluoro-3-piperidinomethyl-2-hexanol (X). A procedure was employed similar to that described above for the preparation of 1,1,1-trifluoro-3-piperidinomethyl-2-butanol (IX). When 10 g. (0.037 mole) of 1,1,1-trifluoro-3-piperidinomethyl-2-hexanol hydrate (Compound VII R = *n*-propyl) was reduced, a colorless oily liquid was obtained. B.p. 92–95° (4 mm.). Yield 4.7 g. (47%).

p-Aminobenzoate. Repeated attempts to purify the *p*-nitrobenzoate derivative of the above alcohol by recrystallization failed. Seven grams (0.016 mole) of the crude *p*-nitrobenzoate hydrochloride in 100 ml. of ethyl alcohol was reduced using 150 mg. of Adams' platinum catalyst and 0.048 mole of hydrogen. After reduction was complete the catalyst was removed by filtration. After many repeated attempts at crystallization of the *p*-aminobenzoate hydrochloride had failed, an alcohol solution of this ester hydrochloride was neutralized with sodium hydroxide, whereupon the color of the solution changed from yellow to a deep orange brown. Upon addition of water a nearly colorless precipitate formed. This was recrystallized from an aqueous alcohol solution and melted at 92–94°. Yield 3.8 g. (63%).

Anal. Calcd. for $C_{19}H_{27}F_3N_2O_2$: C, 61.27%; H, 7.31%. Found: C, 61.42%; H, 7.82%.

p-Aminobenzoate hydrochloride. To 1.4 g. (0.0035 mole) of the free ester was added exactly 37.8 ml. of 0.0924*N* HCl. A white precipitate remained which was washed several times with water and was then dried. It melted at 223–225° (corr.).

Anal. Calcd. for $C_{19}H_{28}F_3N_2O_2Cl$: C, 55.81%; H, 6.89%. Found: C, 55.91%; H, 7.29%.

Acknowledgment. We extend our thanks to Dr. W. C. Fernelius of Pennsylvania State University for suggesting this problem and to Samuel P. Sadtler and Sons, Inc., Philadelphia, who prepared and assisted us in interpreting the infrared spectra.

SYRACUSE 10, N. Y.

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[CONTRIBUTION FROM THE ENTOMOLOGY RESEARCH DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Preparation of Some Substituted α,β-Diphenylacrylic Acids and Related Derivatives

B. H. ALEXANDER AND W. F. BARTHEL

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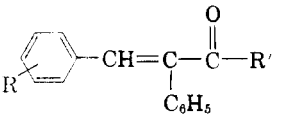
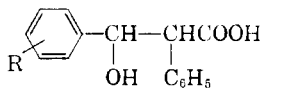
The preparation of a number of compounds related to ethyl β-(3,4-methylenedioxyphenyl)-α-phenylacrylate is described.

A part of the insecticide research program under way in this laboratory is concerned with the synthesis of insect toxicants, synergists, repellents, and attractants. The search for these compounds originally was conducted on an empirical basis, for no relationship between chemical constitution and biological activity was known. However, with the synthesis of many compounds and their subsequent

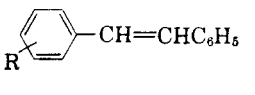
screening against insects, structural leads have been uncovered. These leads, when utilized in the synthesis of additional compounds, have produced a much higher percentage of biologically active compounds than were obtained by the empirical approach.[1] Some esters of tropic acid, for example,



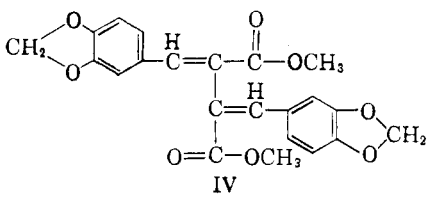
Ia, R = 3,4-CH_2O_2, R′ = OC_2H_5
Ib, R = 3,4-CH_2O_2, R′ = OH
Ic, R = *o*-OCH_3, R′ = OCH_3
Id, R = *p*-OCH_3, R′ = OC_2H_5
Ie, R = *o*-OCH_3, R′ = OH
If, R = 3,4-CH_2O_2, R′ = OCH_3
Ig, R = 3,4-CH_2O_2, R′ = $N(C_2H_5)_2$
Ih, R = *p*-OCH_3, R = $N(C_2H_5)_2$



IIa, R = *p*-OCH_3
IIb, R = 3,4-CH_2O_2



IIIa, R = *p*-OCH_3
IIIb, R = 3,4-CH_2O_2



IV

were found useful as repellents,[2] and a related compound, ethyl β-(3,4-methylenedioxyphenyl)-α-phenylacrylate, Ia,[3] was synthesized and proved to to be an excellent synergist for pyrethrum when tested against lice. With the biological information available on this compound, it was of interest to synthesize compounds related to it and to determine the effect of structural variations on biological activity. The preparation of these compounds is described herein. As indicated by melting point data,[4] the reported acrylic acids are *trans* compounds.

Our attention was first directed toward the synthesis of *beta*-(*p*-methoxyphenyl)tropic acid, IIa. A related compound, *beta*-(3,4-methylenedioxyphenyl)tropic acid, IIb, had previously been prepared in good yield.[3] Most attempts to prepare IIa in a pure state failed, because the compound partially dehydrated on recrystallization from alcohol. However, a pure product was obtained which melted at 136–138° (dec.). When treated with acetic anhydride and sodium acetate at 100°, IIa dehydrated and decarboxylated simultaneously to give the stilbene, IIIa. This decarboxylation was not anticipated, since IIb, when similarly treated, gave the acrylic acid, Ib, in 97% yield,[3] and not 3,4-methylenedioxystilbene, IIIb. Curiously, IIIb was obtained in quantitative yield when the crude chrysanthemumic ester of *alpha*-benzylpiperonyl alcohol was distilled.

Methoxy analogs of Ia (Ic through Ie) were prepared in the same manner as described for the methylenedioxyphenyl compounds.[3] Hydrogenation of these acrylates under pressure with a nickel-kieselguhr catalyst[5] gave the propionates in quantitative yield. The acrylamides were made in the usual way from the acid chlorides. Treatment of 2,3-dipiperonylidenesuccinic acid[6] with methanol and sulfuric acid at 100° gave the dimethyl ester, IV, in high yield.

EXPERIMENTAL

β-(p-Methoxyphenyl)tropic acid (IIa) was prepared as previously described, for the methylenedioxyphenyl compounds,[3] from anisaldehyde and phenylacetic acid. The crude product, yield 43%, was rather difficult to purify because it partially dehydrated when recrystallized from hot ethanol-water (1:1) in the usual way. A pure product was obtained, however, in the following manner.

The crude tropic acid was added to a warm (50°) 50% aqueous alcohol solution with rapid stirring until solution was effected. On cooling precipitation occurred and the isolated crystals when dry melted at 136–138° (dec.).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.47; H, 6.02.

β-(o-Methoxyphenyl)-α-phenylacrylic acid (Ie) was prepared as previously described for the methylenedioxyphenyl compound;[3] recrystallized from ethanol-water (3:1); m.p. 185–187°; yield 59%.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.86; H, 5.80.

3-(o-Methoxyphenyl)-2-phenylacrylic acid, methyl ester (Ic) was prepared by refluxing the acid with 5% methanolic hydrogen chloride; recrystallized from methanol; m.p. 100–101°; yield 86%.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.69; H, 6.14.

3,4-Methylenedioxystilbene (IIIb) was produced in quantitative yield when the crude chrysanthemumate of *alpha*-benzylpiperonyl alcohol[7] was distilled at 145–180° at 0.2 mm. pressure in a short-path still; recrystallized from 95% ethanol; m.p. 93–94° (lit. 95–96°).[8]

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.04; H, 5.41. Found: C, 79.91; H, 5.32.

4-Methoxystilbene (IIIa) was prepared from beta-(*p*-methoxyphenyl)tropic acid.[3] The acid, 89 g., acetic anhydride, 200 ml., and anhydrous sodium acetate, 50 g., were stirred on the steam bath at 100° for 4 hr. The mixture, while hot, was poured into 1 kg. of cracked ice and water with stirring. After standing overnight, the mixture was filtered and the crystals were washed with cold water;

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recrystallized from 95% ethanol; m.p. 135–136° (lit. 132°)[9]; yield 75%.

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.94; H, 6.93.

β-(p-Methoxyphenyl)-α-phenylacrylic acid, ethyl ester (Id) was prepared in the usual way by refluxing the acid with 5% ethanolic hydrogen chloride; recrystallized from ethanol; m.p. 48–50°; yield 51%.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.79; H, 6.30.

3-(p-Methoxyphenyl)-2-phenylpropionic acid, ethyl ester (Id dihydro) was prepared by hydrogenation of the acrylate (Id), 35 g , ethanol, 120 ml., and nickel-kieselguhr catalyst,[5] 5 g. at 2000 p.s.i. and at 130° for approximately 1 hr.; recrystallized from 95% ethanol; m.p. 57–59°; yield quantitative.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.60; H, 7.29.

3-(o-Methoxyphenyl)-2-phenylpropionic acid, methyl ester (Ic dihydro) was prepared in the same manner as the ethyl ester (described above); b.p. 147–155°/0.5 mm., n_D^{25}° 1.5538; yield quantitative.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 76.01; H, 6.86.

3-(3,4-Methylenedioxyphenyl)-2-phenylpropionic acid, methyl ester (If dihydro) was prepared as described above; b.p. 162–195°/0.2 mm., n_D^{25}° 1.5636; yield quantitative.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.81; H, 5.67. Found: C, 71.06; H, 5.94.

3-(3,4-Methylenedioxyphenyl)-2-phenylpropionic acid, ethyl ester (Ia dihydro) was prepared as described above; b.p. 161–190°/0.2 mm., n_D^{25} 1.5552; yield quantitative.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.10; H, 6.41.

2,3-Dipiperonylidenesuccinic acid, dimethyl ester (IV) was prepared by refluxing 2,3-dipiperonylidenesuccinic acid,[6] 83 g., sulfuric acid, 50 g., and methanol, 1 l., for 6 hr. The product was isolated in the usual way; recrystallized from ethanol; m.p. 181–182°; yield quantitative.

Anal. Calcd. for $C_{22}H_{18}O_8$: C, 64.39; H, 4.42. Found: C, 63.83; H, 4.70.

N,N-Diethyl-β-(3,4-methylenedioxyphenyl)-α-phenylacrylamide (Ig) was prepared in the usual way by reacting the acid chloride with diethylamine; recrystallized from 95% ethanol; m.p. 128–129°; crude yield quantitative.

Anal. Calcd. for $C_{20}H_{21}NO_3$: N, 4.33. Found: N, 4.07.

N,N-Diethyl-β-(p-methoxyphenyl)-α-phenylacrylamide (Ih) was prepared as described above; recrystallized from ethanol-water (4:1); m.p. 68–70°; crude yield quantitative.

Anal. Calcd. for $C_{20}H_{23}NO_2$: N, 4.53. Found: 4.77.

Acknowledgment. All microanalyses were performed by Kathryn Gerdeman, of the Chemistry Department, University of Maryland.

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

A Preparation and Certain Properties of 2-Carbomethoxy-*N*-methylgranatonine

STEPHEN P. FINDLAY*

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The preparation of racemic 2-carbomethoxy-*N*-methylgranatonine is described, and certain of its physical and chemical properties are compared with those of racemic 2-carbomethoxytropinone.

Succindialdehyde combines with methylamine and the half methyl ester (II) of β-ketoglutaric anhydride (I), the principal product being racemic 2-carbomethoxytropinone (VI and its mirror image).[1] The readiness with which this variation of Robinson's biological synthesis[2,3] occurs made it seem probable that an analogous condensation in which glutaraldehyde, now obtainable commercially,[4] was used in the place of succindialdehyde would give racemic 2-carbomethoxy-*N*-methylgranatonine (3 - keto - 2 - carbomethoxy - 9 - methyl - 9 - azabicyclo[3.3.1]nonane)(III) with comparable ease; and it was thought that this compound, which has not been reported before, would permit some instructive comparisons with racemic 2-carbomethoxytropinone and that it might constitute a valuable intermediate in the synthesis either of analgesics like cocaine and psicaine[5] or of certain derivatives of cyclooctane or of both.

By this procedure 2-carbomethoxy-*N*-methylgranatonine (III) was indeed obtained, but the yield realized (*ca.* 25%) was disappointing, being no greater than half that of 2-carbomethoxytropinone.[1] The large quantities of colored by-products likewise isolated, are, because of their solubility in aqueous alkali, very probably β-keto esters also. It is pertinent here to note that, although *trans* fusion of the rings in the reaction leading to 2-carbomethoxytropinone (VI) is almost certainly

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