TABLE II

PREPARATION OF N-SUBSTITUTED PEPTIDE ESTERS

	Yield, %	M.p., °C. (cor.)	$[\alpha]^{24}D$ (ethanol)	Formula	Analyses,[g] % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ethyl carbobenzoxyglycyl-DL-phenylalaninate[a]	86	91–92	.....							
Ethyl carbobenzoxyglycyl-L-tyrosinate[b]	77	125–127	+18.4 (c = 5)							
Ethyl carbobenzoxy-L-leucylglycinate[c]	70	103–104	−25.6 (c = 5)							
Ethyl dicarbobenzoxy-L-lysylglycinate[d]	58	89–91	−12.0 (c = 5)							
Methyl carbobenzoxy-L-leucyl-L-leucinate[e]	29	97–98.5	−35.3 (c = 10)							
Ethyl carbobenzoxy-L-leucyl-L-tyrosinate	52	115–117	−15.2 (c = 5)	$C_{25}H_{32}N_2O_6$	65.77	7.07	6.14	65.68	7.22	6.28
Ethyl carbobenzoxy-L-leucyl-DL-phenylalaninate	38	84–87	.....	$C_{25}H_{32}N_2O_5$	68.16	7.16	6.36	[h]	7.25	6.24
Ethyl carbobenzoxy-DL-alanyl-DL-phenylalaninate	48	114–116	.....	$C_{22}H_{26}N_2O_5$	66.31	6.58	7.03	66.22	6.65	7.17
Ethyl carbobenzoxyglycyl-DL-phenylalanyl-glycinate[f]	86	132–133	.....	$C_{23}H_{27}N_3O_6$	62.57	6.17	9.52	62.32	6.24	9.64
Ethyl phthalylglycyl-DL-phenylalaninate	68	149–150	.....	$C_{21}H_{20}N_2O_5$	66.30	5.30	7.37	66.28	5.36	7.43
Ethyl phthalylglycyl-L-tyrosinate	60	163–164	+43.0 (c = 2)	$C_{21}H_{20}N_2O_6$	63.63	5.05	7.07	63.40	5.10	7.27
Ethyl phthalylglycyl-L-leucinate	62	139–140	−24.5 (c = 2)	$C_{18}H_{22}N_2O_5$	62.41	6.40	8.09	62.20	6.44	8.05
Ethyl phthalyl-DL-alanyl-DL-valinate	40	110–130	.....	$C_{18}H_{22}N_2O_5$	62.41	6.40	8.09	62.34	6.56	8.26

[a] H. Neurath, *et al.*, *J. Biol. Chem.*, **170**, 221 (1947), give m.p. 90–91° (cor.). [b] M. Bergmann and J. S. Fruton, *ibid.*, **118**, 405 (1937), give m.p. 118°. [c] M. Bergmann, *et al.*, *ibid.*, 111, 225 (1935), give m.p. 103-104°; M. A. Nyman and R. M. Herbst, *J. Org. Chem.*, **15** 108 (1950), give m.p. 99° and $[\alpha]^{25}D$ −26.8° (c = 2.6 ethanol). [d] M. Bergmann, *et al.*, *Z. physiol. Chem.*, **224**, 26 (1934), give m.p. 90°. [e] M. A. Nyman and R. M. Herbst, *ibid.*, give m.p. 97–98°. [f] Prepared from carbobenzoxyglycyl-DL-phenylalanine and ethyl glycinate. [g] We are indebted to Dr. J. A. Kuck and his staff of these laboratories for the microanalyses. The values reported are the average of two values differing by not more than 0.30. [h] A satisfactory carbon value was not obtained on this compound.

was washed with water and the product which had crystallized out was filtered off and washed with 3% sodium bicarbonate solution; wt. 5.29 g. (55% yield), m.p. 91–92°. The toluene layer was separated from the filtrate, washed rapidly with 3% sodium bicarbonate solution and diluted until cloudy with petroleum ether and cooled to crystallize a second crop of material; wt. 3.14 g. (33% yield); m.p. 90–91°. The two crops were combined and recrystallized from aqueous ethanol to give 8.25 g. (86%) of product melting at 91–92°.

Ethyl Carbobenzoxy-L-leucylglycinate.—A solution of 5.30 g. (0.02 mole) of carbobenzoxy-L-leucine and 2.04 g. (0.02 mole) of triethylamine in a mixture of 25 cc. of toluene and 25 cc. of chloroform was cooled to −5° and 2.41 g. (0.02 mole) of isovaleryl chloride added. After 1.5 hours a second, precooled solution of 2.79 g. (0.02 mole) of ethyl glycinate hydrochloride and 2.04 g. (0.02 mole) of triethylamine in 50 cc. of chloroform was added, and the reaction mixture was stored overnight at 8°. The organic solution was washed with water and with 3% sodium bicarbonate solution and diluted until cloudy with petroleum ether. On cooling, the product separated as colorless crystals; wt. 2.17 g. (31%), m.p. 103–104°. Concentration of the mother liquor almost to dryness in a stream of air and rediluting with petroleum ether gave a second crop of crystalline product; wt. 2.98 g. (43%); m.p. 102–103°. The two crops were combined and recrystallized from aqueous ethanol to give 4.90 g. (70%) of pure product melting at 105–106°.

STAMFORD, CONNECTICUT RECEIVED MAY 31, 1951

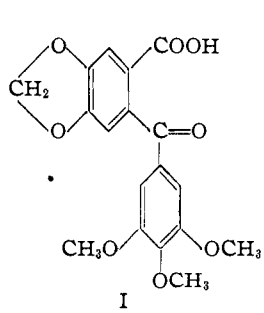
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BOSTON UNIVERSITY]

Synthesis of 2-(3′,4′,5′-Trimethoxybenzoyl)-piperonylic Acid[1,2]

BY WALTER J. GENSLER AND CARLOS M. SAMOUR

A synthesis for 2-(3′,4′,5′-trimethoxybenzoyl)-piperonylic acid is described according to the following sequence: homopiperonylamine, N-(trimethoxybenzoyl)-homopiperonylamine, 1-(3′,4′,5′-trimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline, 2-(3′,4′,5′-trimethoxybenzoyl)-4,5-methylenedioxystyrene and 2-(3′,4′,5′-trimethoxybenzoyl)-piperonylic acid. The over-all yield for the four steps is 60%.

In view of the possibility of elaborating picropodophyllin (II) or the related podophyllotoxin[3] from 2-(3′,4′,5′-trimethoxybenzoyl)-piperonylic acid (I), a convenient source of this keto acid would be desirable. Although 2-(3′,4′,5′-trimethoxybenzoyl)-piperonylic acid (I) had been obtained before, not only from picropodophyllin (II)[4] itself, but also from a synthetic dihydronaphthalene derivative[5] and from several derivatives of 1-(3′,4′,5′-trimethoxyphenyl)-6,7-methylenedioxyisoquinoline,[6] none of the paths constituted an attractive preparative method. We wish now to report on a practical synthesis of keto-acid (I).[7]



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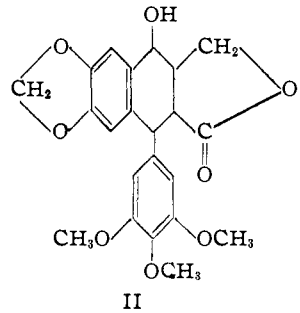


II

(1) This work was supported by American Cancer Society Grant-in-Aid No. CBC-6 as recommended by the Committee on Growth of the National Research Council.

(2) A summary of the material in this paper was presented in Boston, Mass., on April 3, 1951, before the Division of Organic Chemistry of the American Chemical Society.

(3) Podophyllotoxin, a tumor-damaging substance, is currently of interest as a potentially useful anti-cancer agent. For example, see the report by J. Leiter, V. Downing, J. L. Hartwell and M. J. Shear, *J. Nat. Cancer Inst.*, **10**, 1273 (1950).

(4) E. Späth, F. Wessely and E. Nadler, *Ber.*, **66**, 125 (1933).

(5) R. D. Haworth and T. Richardson, *J. Chem. Soc.*, 348 (1936). See also R. D. Haworth and J. R. Atkinson, *ibid.*, 797 (1938).

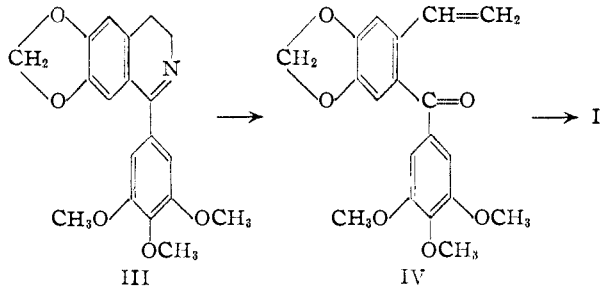
(6) W. Reeve and W. M. Eareckson, III, THIS JOURNAL, **72**, 5195 (1950).

(7) A brief account of this work has appeared, *ibid.*, **72**, 3318 (1950). In the preliminary report, reference to the work of Haworth and Richardson (ref. 5) was inadvertently omitted.

The structural relationship between 1-(trimethoxyphenyl) - 6,7 - methylenedioxy - 3,4 - dihydroisoquinoline (III) and trimethoxybenzoylpiperonylic acid (I) suggested that the former compound might serve in some way as a source for the latter. It became evident, however, that if the transformation of III to I were to be effected by oxidation, a structural feature would have to be introduced at the isoquinoline 3- or 4-position which would permit oxidative cleavage to occur between these positions more rapidly than oxidative disruption of the relatively reactive benzenoid rings.[8]

On considering means to achieve this end, a series of reactions was recalled in which 6,7-methylenedioxy-3,4-dihydroisoquinoline was converted in several steps to 2-formyl-4,5-methylenedioxystyrene.[9] The analogous series starting with 1-(3′,4′,5′-trimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline would lead to 2-(3′,4′,5′-trimethoxybenzoyl)-4,5-methylenedioxystyrene (IV), which compound appeared to offer an excellent opportunity for oxidative cleavage at the proper point.

Examination of the reactions leading to 2-formyl-4,5-methylenedioxystyrene[9] showed first, that either



a methylating agent or a base was involved in each of the several steps and, second, that there was no reason to expect either of the two reagents to act adversely on any of the steps. This brought out the possibility of combining all the steps into a single-stage process by treating the dihydroisoquinoline with methyl sulfate and excess alkali. The possibility was realized; and eventually conditions were found which permitted transformation of the dihydroisoquinoline (III) directly to the vinyl ketone (IV) in 85–98% yield.[10]

Selective oxidation of the vinyl ketone (IV) could now be carried out, the desired keto-acid (I) being obtained in moderate conversion (55%) although in high yield (85%). The keto-acid was identical with the same compound obtained from picropodophyllin (II). Decarboxylation led to the known 3,4,5-trimethoxy-3′,4′methylenedioxy benzophenone,[4] and esterification to the keto-ester

The over-all yield in the four steps from homopiperonylamine (from which dihydroisoquinoline III was prepared by way of the Bischler Napieralski process) to 2-(trimethoxybenzoyl) piperonylic acid (I) was 60%.

Experimental[11]

1-(3′,4′,5′-Trimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (III).—This material was prepared according to the following sequence: piperonal, piperonylidene–nitromethane, homopiperonylamine, N-(trimethoxybenzoyl)-homopiperonylamine and 1-(3′,4′,5′-trimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (III).

Piperonal was converted to piperonylidene-nitromethane by allowing a solution of 90 g. of piperonal (0.60 mole), 39 g. of nitromethane (0.64 mole) and 2 ml. of 70% aqueous ethylamine in 250 ml. of absolute ethanol to stand for 2 days at room temperature.[12] The mixture, containing long yellow needle-like crystals, was cooled and filtered, and the solids washed on the funnel with cold alcohol, and dried. The piperonylidene-nitromethane weighed 112.5 g. (97%) and melted without further purification at 162.0–163° (reported[12] m.p. 158°).

The report that lithium aluminum hydride was effective in the conversion of ω-nitrostyrenes to phenylethylamines[13] led us to adopt this method for the preparation of homopiperonylamine. However, in view of the recent publication of Erne and Ramirez (see ref. 13), a detailed description of the reaction is omitted here. It should be noted that the use of dioxane as solvent for the nitrostyrene permitted dispensing with the Soxhlet extraction procedure; and that although the product homopiperonylamine (b.p. 82° (0.1 mm.) was obtained in 60% yield, as compared with 86% reported by Erne and Ramirez, the reaction time was shorter (65 minutes *vs.* 8 hours) and larger amounts of starting material could be more conveniently processed.

Acylation of homopiperonylamine with trimethylgalloyl chloride was carried out under Schotten–Baumann conditions. In a 500-ml. flask provided with a stirrer was placed 11.5 g. (0.07 mole) of homopiperonylamine and 250 ml. of 2% sodium hydroxide solution. Powdered 3,4,5-trimethoxybenzoyl chloride, prepared according to Reeve and Sterling (see ref. 8), was added portionwise to the cooled and vigorously stirred solution over a 1-hour period. After an additional 2.5 hours of stirring, the reaction mixture was filtered, the solids washed with water and dried *in vacuo*. Decolorization of the crude amide (22.6 g.) in absolute alcohol solution, followed by a single crystallization from the same solvent afforded 20.1 g. (80%) of N-(trimethoxybenzoyl)-homopiperonylamine, m.p. 135.2–135.7° (reported[6] m.p. 135.5–136°).

Anal. Calcd. for $C_{19}H_{21}O_6N$: C, 63.5; H, 5.9; N, 3.9. Found: C, 63.5; H, 5.9; N, 3.9.

The Bischler–Napieralski cyclization of the amide to dihydroisoquinoline (III) was modelled after a procedure given by Haworth, Perkin and Rankin[14] for the preparation of a related dihydroisoquinoline.

A mixture of 6 g. (0.0157 mole) of N-(trimethoxybenzoyl)-homopiperonylamine, 12 ml. of phosphorus oxychloride and 30 ml. of toluene was boiled for 2 hours under a condenser provided with a calcium chloride drying tube. Petroleum ether was added to the cooled reaction mixture, which was

(8) Direct oxidation of the dihydroisoquinoline (III) yielded negative results in our hands. Reeve and Bareckson (ref. 6) did obtain the keto-acid in this reaction (and in other related reactions) although in low yield. The reported lack of success in the oxidation of 2-(3′,4′,5′-trimethoxybenzoyl)-4,5-methylenedioxytoluene to keto-acid (I) [W. Reeve and J. D. Sterling, Jr., THIS JOURNAL, **71**, 3657 (1949)] was also considered to be pertinent to this conclusion. W. von E. Doering and J. A. Berson [*ibid.*, **72**, 1118 (1950)] did realize an oxidative conversion closely related to the last example, but again the yield was low. E. Leupin and H. Dahn [*Helv. Chim. Acta*, **30**, 1945 (1947)] oxidized a substituted 1-phenyl-3-,4-dihydroisoquinoline to a keto-acid with dichromate in approximately 12% yield.

(9) This series was carried through in connection with the investigation of hydrastinine. See H. Decker, *et al.*, *Ann.*, **395**, 299, 321 (1913); M. Freund, *Ber.*, **22**, 2329 (1889). An analogous series was reported in connection with cotarnine. W. Roser, *Ann.*, 249, 156 (1888); M. Freund and F. Becker, *Ber.*, **36**, 1521 (1903); H. Decker and P. Becker, *Ann.*, **395**, 328 (1913). See also W. H. Perkin, Jr., *J. Chem. Soc.*, **109**, 815 (1916).

(10) A report presenting evidence for the reaction path in the single-stage conversion of III to IV is being prepared for publication.

(11) All melting points are corrected. Analyses by Carol K. Fitz, 115 Lexington Ave., Needham Heights 94, Mass.

(12) E. Knoevenagel and L. Walter, *Ber.*, **37**, 4502 (1904). The use of ethylamine rather than methylamine hydrochloride and sodium carbonate offers definite advantages.

(13) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **70**, 3738 (1948); K. E. Hamlin and A. W. Weston, *ibid.*, **71**, 2210 (1949); F. A. Ramirez and A. Burger, *ibid.*, **72**, 2781 (1950); F. Benington and R. D. Morin, *ibid.*, **73**, 1353 (1951); M. Erne and F. Ramirez, *Helv. Chim. Acta*, **33**, 912 (1950).

(14) R. D. Haworth, W. H. Perkin, Jr., and J. Rankin, *J. Chem. Soc.*, **125**, 1686 (1924).

then allowed to stand in the ice-bath for 2 hours. After decanting the toluene–petroleum ether layer, 50 ml. of alcohol was added and the mixture, warmed on the steam-bath, made alkaline with alcoholic potassium hydroxide. The alkaline mixture was poured over crushed ice and water, and allowed to stand for 2 hours. The solid was collected, washed with water, and dried *in vacuo*. Recrystallization of the crude product (11.0 g.) from benzene–petroleum ether yielded 10.6 g. (93%) of colorless crystalline 1-(3′,4′,5′-trimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (III), m.p. 160.2–160.6° (reported[6] m.p. 159.5–160°). Further crystallization did not raise the melting point.

Anal. Calcd. for $C_{19}H_{19}O_5N$: C, 66.8; H, 5.6; N, 4.1. Found: C, 66.7; H, 5.8; N, 4.1.

In one experiment the yield of product after purification was 97.4%.

2-(3′,4′,5′-Trimethoxybenzoyl)-4,5-methylenedioxystyrene (IV) from 1-(3′,4′,5′-Trimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (III).—A stirred mixture of 10.23 g. (0.03 mole) of dihydroisoquinoline (III), 24 ml. of methyl sulfate (0.254 mole), 150 ml. of 40% sodium hydroxide solution and 150 ml. of water was heated on the steam-bath under a condenser for 18 hours. The cooled reaction mixture, after acidification with hydrochloric acid, was filtered, and the precipitate washed with water and dried *in vacuo*. Pale yellow crystalline 2-(3′,4′,5′-trimethoxybenzoyl)-4,5-methylenedioxystyrene (IV) obtained in this way showed m.p. 139–139.8° and weighed 10.08 g. (98%). A sample prepared for analysis by crystallizing material obtained in an earlier experiment from methanol (90% recovery) showed m.p. 139.2–139.8°. Benzene–petroleum ether was later found to be a more satisfactory solvent mixture for crystallization.

Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.7; H, 5.3. Found: C, 66.6; H, 5.3.

2-(3′,4′,5′-Trimethoxybenzoyl)-piperonylic Acid (I).—Five grams of 2-(3′,4′,5′-trimethoxybenzoyl)-4,5-methylenedioxystyrene (0.0146 mole) was dissolved in 300 ml. of acetone contained in a 1 l. three-necked flask fitted with stirrer and condenser. Solid potassium permanganate (8.84 g. or 0.056 mole) was added portionwise over a period of 1 hour to the stirred and boiling acetone solution. At the disappearance of the permanganate pink color, the condenser was set for distillation, and the acetone removed. Water (150 ml.) was added to the residual solids, and gaseous sulfur dioxide bubbled through the cooled mixture until the brown precipitate disappeared. The cold mixture was filtered and, in order to effect a separation of product and unreacted starting material, the solids were treated with 50 ml. of 2% sodium hydroxide solution. The solid obtained on filtering the alkaline mixture, after washing and drying *in vacuo*, weighed 1.85 g. One crystallization of this material from benzene–petroleum ether furnished 1.75 g. (35% recovery) of 2-(3′,4′,5′-trimethoxybenzoyl)-4,5-methylenedioxystyrene (IV), m.p. 138.5–139.5°.

Acidification of the alkaline filtrate with dilute hydrochloric acid and filtration of the cold mixture afforded crude keto-acid (I) which on drying *in vacuo* weighed 3.05 g. and melted at 211.5–213°.

Purification was effected by decolorizing the crude product in methanol solution followed by crystallization. 2-(3′,4′,5′-Trimethoxybenzoyl)-piperonylic acid (I), m.p. 215.2–215.7° (2.9 g.), was obtained in 85% corrected or 55% uncorrected yield.

Anal. Calcd. for $C_{18}H_{16}O_8$: C, 60.0; H, 4.5. Found: C, 60.0; H, 4.5.

The same material obtained from picropodophyllin (II, m.p. 225–226°) by oxidation according to Späth, *et al.*,[4] melted at 213.4–215.4° and, on admixture with the synthetic material, at 214.4–215.7°. Decarboxylation of the synthetic keto-acid (I) by following essentially the direction of Späth, *et al.*,[4] furnished 3,4,5-trimethoxy-3′,4′-methylenedioxybenzophenone, m.p. 125.3–126.5° (reported[4] m.p. 125–127°).

Ethyl 2-(3′,4′,5′-Trimethoxybenzoyl)-piperonylate.—A solution of 8.0 g. (0.022 mole) of the keto-acid (I) in 350 ml. of absolute ethanol containing 7 ml. of concentrated sulfuric acid was boiled for 3 hours. Most of the solvent was removed under reduced pressure, and the concentrated solution, after dilution with water, was neutralized (cooling) with 10% aqueous sodium bicarbonate solution. Product was isolated by extracting the neutralized solution with ether, and evaporating the ether. The methanol solution of the residual material was first heated with decolorizing carbon, then concentrated, and water added dropwise until a slight turbidity was observed. Addition of a small volume of methanol led to a clear solution which was allowed to stand first at room temperature and then in the refrigerator.

The colorless crystals were collected and washed on the funnel with cold aqueous methanol and dried *in vacuo*. Crystallization of the material so obtained (7.5 g., m.p. 95–96°) from aqueous methanol yielded 7.0 g. (81%) of ethyl 2-(3′,4′,5′-trimethoxybenzoyl)-piperonylate, m.p. 96.5–97°.

Anal. Calcd. for $C_{20}H_{20}O_8$: C, 61.9; H, 5.2. Found: C, 61.8; H, 5.1.

BOSTON, MASSACHUSETTS RECEIVED JUNE 4, 1951

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Ethanolamides of Some Mono- and Dicarboxylic Acids

BY ARTHUR P. PHILLIPS

A series of ethanolamides has been made from an assorted group of mono- and di-carboxylic acids. A noteworthy difference in chemical properties was observed during attempts to prepare the bis amides and the imides from phthalic acid and succinic acid derivatives. The reaction of ethanolamine with either dimethyl phthalate or phthalic anhydride gave only the cyclic imide, while in contrast diethyl succinate or succinic anhydride gave only the open chain bis-amide. This divergence in behavior is attributed to the steric relationships in the acids concerned.

In connection with earlier investigations of acyl migrations in aminoethanols[1,2] a series of ethanolamides was prepared from a variety of carboxylic acids. Some of these were made for use in rearrangement studies and many have been screened for certain types of pharmacological activity.

Most of these amides were obtained as in the earlier work[1] by a method related to that of D'Alelio and Reid.[3] A mixture of the carboxylic acid methyl or ethyl ester with one to three molecular equivalents of ethanolamine for *each* ester group was refluxed in a metal-bath at or above 160° for varying periods of time.

Compound IX,[4] Table I (B), was best made from *p*-nitrobenzoyl chloride and excess of ethanolamine. Catalytic hydrogenation of IX using Adams catalyst gave X, *p*-amino-N-(β-hydroxyethyl)-benzamide.

N-(β-Hydroxyethyl)-*p*-toluenesulfonamide, XI of Table I (B), was prepared by the interaction of ethanolamine with *p*-toluenesulfonyl chloride in

(1) A. P. Phillips and R. Baltzly, THIS JOURNAL, **69**, 200 (1947).
(2) A. P. Phillips and A. Maggiolo, *ibid.*, **72**, 4920 (1950).
(3) G. F. D'Alelio and E. E. Reid, *ibid.*, **59**, 111 (1937).
(4) H. Brintzinger and H. Koddebusch, *Ber.*, **82**, 201 (1949).