Pyrex tubes using 100 g. of total monomers. Appropriate amounts (Table IV) of styrene, methyl acrylate and benzoyl peroxide were weighed into a heavy-walled Pyrex tube 1″ in diameter, 2′ long and constricted 3″ below the open end. The solution was cooled in a Dry Ice-bath and a suitable volume of cooled vinyl chloride was added. The tube was sealed, allowed to warm to room temperature and the amount of vinyl chloride added determined by weight difference. The tube was immersed vertically in a water-bath regulated to 50 ± 0.05°. When a slight increase in viscosity was observed the tube was removed, cooled to room temperature and weighed. No vinyl chloride was lost in either experiment. The tube was cooled in a Dry Ice-bath, the constricted end opened and the whole allowed slowly to warm to room temperature. The solution was then poured into 500 ml. of 2B ethanol vigorously agitated in a Waring blender. The resulting fine powder was filtered on a Buchner, washed with three fresh 1000-ml. portions of alcohol. After drying the product for twenty-four hours at 50° in a circulating air oven, it was weighed, analyzed in duplicate for chlorine by the Thompson–Oakdale method and for carbon and hydrogen by the micro method. Polymerization times, conversions and analytical data are summarized in Table IV.

Vinyl Chloride–Styrene–Acrylonitrile.—These samples were prepared by mass polymerization in screw-cap 200-ml. pressure bottles using 60 g. of total monomers. The bottle was charged by adding appropriate weights (Table IV) of styrene, acrylonitrile and benzoyl peroxide to the bottle, cooling and adding vinyl chloride as before. The bottle was rotated end over end in a constant temperature water-bath first at 50°, then at 25° for the times

shown in Table IV. Weight losses were 0–0.2 g. for the experiments. After venting vinyl chloride, the slightly viscous solution was poured into 500 ml. of stirred 2B ethanol and the bottle and cap rinsed with two 10-ml. portions of benzene. The resulting fine powder was filtered on a Buchner funnel, washed with three 1000-ml. portions of fresh ethanol and dried in a circulating air oven at 60° for forty-eight hours. The sample was weighed, analyzed in duplicate for chlorine by the Parr bomb method and for nitrogen by the Kjeldahl method. Data for these experiments are summarized in Table IV.

Summary

Monomer–polymer composition curves for the systems vinyl chloride–styrene, vinyl chloride–methyl acrylate and vinyl chloride–acrylonitrile have been determined. Coincidence of the solution and emulsion curves for the system styrene–vinyl chloride provides additional evidence for the oil phase mechanism of emulsion polymerization. Numerical values for monomer reactivity ratios for these systems are reported. Using these data an experimental investigation of the validity of the tripolymer equation was made. Good agreement was obtained between calculated compositions and compositions actually obtained.

[CONTRIBUTION FROM SMITH, KLINE AND FRENCH LABORATORIES]

Analgesics. II. A New Synthesis of Aminophthalidylalkanes

BY GLENN E. ULLYOT, HERBERT W. TAYLOR, JR., AND NORMAN DAWSON

Recently we reported[1] the synthesis of a series of aminophthalidylalkanes, one of which, 1-amino-1-phthalidylpropane hydrochloride, showed considerable activity as an analgesic agent. The method of synthesis resulted chiefly in the lower melting racemic form, isomer B, but both racemic forms (isomers A and B) were isolated by careful fractional crystallization. Pharmacological tests indicated a difference in the toxicity and analgesic activity of these isomers, isomer A being more active and more toxic. For this reason, a need arose for a more convenient method of preparing sufficient amounts of isomer A for further pharmacological and clinical studies. This was accomplished according to Scheme I; only isomer A (VIII) was obtained.

In the synthesis previously reported, the asymmetry of the carbon atom next to the benzene ring was established first. The presence of this asymmetric center undoubtedly operated during the formation of the second asymmetric carbon center, so that there resulted unequal amounts of the two racemic forms of the nitro compound and, consequently, of the amine hydrochloride. In the synthesis reported here, our results may be

accounted for by the reversal of the order of establishment of the asymmetric centers.

On attempting to proceed directly from o-carboxybutyrophenone without recourse to ester formation, it was found that ethyl nitrite failed to react with an ethereal solution of the ketone in the presence of anhydrous hydrogen chloride. This may have been because the keto acid existed chiefly as a lactol; in any event, the ester V was readily converted to VI.

Catalytic reduction of α-isonitrosoalkylphenyl ketones in the presence of three equivalents of anhydrous hydrogen chloride in absolute alcohol[2] has been shown to proceed first at the isonitroso group and then at the carbonyl group. Catalytic reduction of VI was readily effected; the course of the hydrogen uptake is shown in Fig. 1.

Unless the crude V was thoroughly washed with bicarbonate, considerable decomposition occurred during distillation and resulted in a material contaminated with propylidenephthalide (III). However, even after taking into consideration the amount of propylidenephthalide present in various batches of keto ester, treatment of this material with ethyl nitrite did not result in complete conversion into VI except in the case of ester no. 2

(1) Ullyot, Stehle, Zirkle, Shriner and Wolf, *J. Org. Chem.*, **10**, 429 (1945).

(2) Hartung, THIS JOURNAL, **53**, 2248 (1931).

SCHEME I
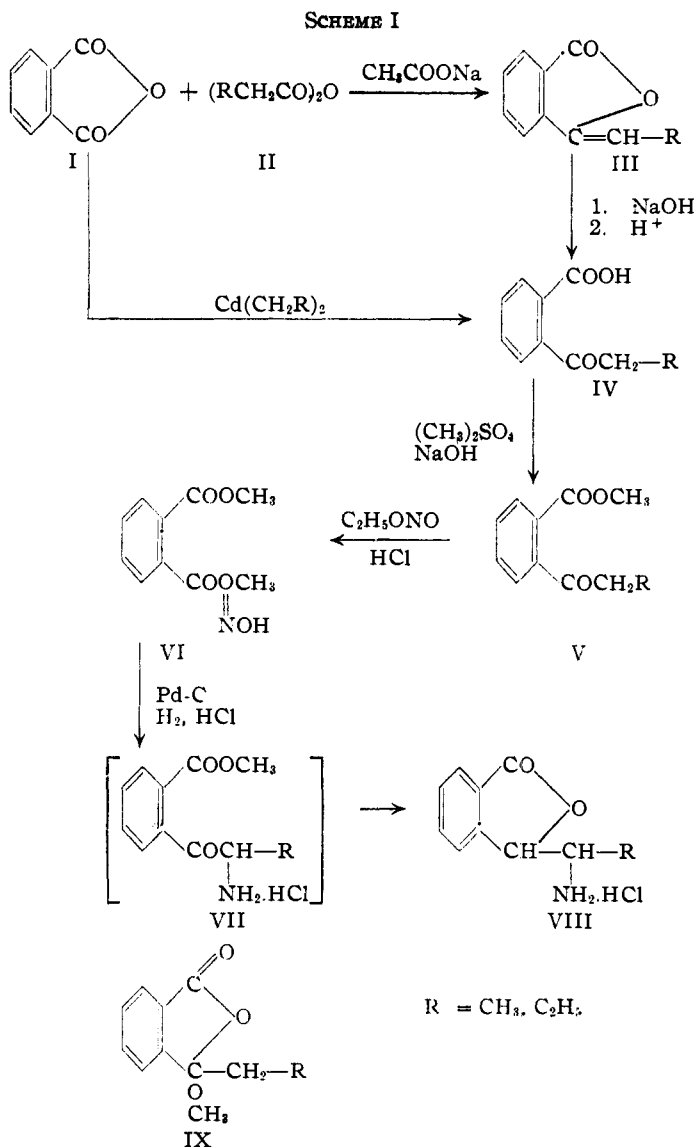
(see Table I). This may have been due to the presence of pseudo-ester (IX). Preparation of ester under conditions which might have been expected to lead to only IX[3] resulted in a product which gave a 55% yield of VI (Table I, no. 7). Absorption spectra data (Fig. 2) showed that the ester contained no propylidenephthalide and, therefore, it was at first thought to be a mixture of V and IX. However, the absorption curve of this ester (Fig. 2, curve f) was inappreciably different from that of "pure" V (Fig. 2, curve d), as was true of Compound V (Fig. 2, curve e) which was prepared from IV and diazomethane, a condition most likely to give only V. The significance of absorption spectra data and the isonitroso reaction with respect to normal and pseudo esters needs further clarification.

(3) Newman and Lord, THIS JOURNAL, **66**, 731 (1944); Auwers and Heinze. Ber.. **52**, 584 (1919).

Our inference as to the presence of pseudo ester and its effect on the isonitroso reaction is based on the fact that when ester no. 2 was used in the isonitroso reaction, the reaction was complete and there were no mechanical losses, and on the fact that ester no. 7, which contained no propylidenephthalide, gave only a 55% yield of the isonitroso derivative.

The synthesis of 1-amino-1-phthalidylethane, isomer A (VIII, R = CH_3), also was accomplished according to Scheme I, thus indicating the general applicability of the procedure.

Experimental[4]

o-Carboxybutyrophenone (IV, R = $-C_2H_5$).
—This compound was prepared in two ways. (A) The acid was prepared by the general procedure of De Benneville[5a] from dipropylcadmium and phthalic anhydride in a yield of 70%, m. p. 89° (lit.[1] 87–89°). (B) 3-Propylidenephthalide was prepared[5b,c] and hydrolyzed to the keto acid. Sodium acetate (164 g., 2.0 moles), n-butyric anhydride (632 g., 4.0 moles) and phthalic anhydride (296 g., 2.0 moles) were heated at 180–190° for seven hours, excess reagents were removed by distillation in vacuo, and the mixture was diluted with water and made alkaline with ammonium hydroxide. The propylidenephthalide, after extraction by chloroform and distillation, was obtained in a 70% yield, b. p. 143–145° (5 mm.) (lit.,[5c] b. p. 169–170° (12 mm.), $n^{20}D$ 1.586). The propylidenephthalide was hydrolyzed by warming it to 70° for thirty minutes in 50% isopropanol containing one equivalent of sodium hydroxide. Acidification of the deep red solution gave the product as an orange solid. This was obtained in pure condition in a 75% yield by dissolving it in sodium bicarbonate, adding sufficient acid to liberate 2% of the dissolved material, and extracting the mixture with chloroform. Acidification then precipitated a product which no longer gave a red color upon dissolving it in alkali; m. p. 86–89°. Evaporation of the chloroform extracts left an oil which distilled over the range 125–160° (3 mm.), but chiefly over the range of 125–140° (3 mm.). This gave a bright red solution when dissolved in 10% alkali and a violet-red color when dissolved in sulfuric acid. It may have been impure 2-ethyl-1,3-indanedione,[6] but it failed to give a 2,4-dinitrophenylhydrazone and did not crystallize. The indanedione is reported to boil at 135–140° (7 mm.) and to melt at 53–55°.[6]

Methyl Butyrophenone-o-carboxylate(V, R = $—C_2H_5$).
—o-Carboxybutyrophenone (640 g., 3.33 moles) was esterified in a solution composed of methanol (1200 cc.) and sodium hydroxide (160.2 g., 3.99 moles) in water (240 cc.) by the slow addition with stirring of dimethyl sulfate (506 g., 3.99 moles). The product was extracted by ether, after removal of half the alcohol by distillation and dilution with water, washed thoroughly with one molar sodium bicarbonate solution and with a saturated sodium chloride solution, and dried over sodium sulfate.

(4) The analyses were carried out by Miss Lillian Sillano and Mrs. Gertrude Carney.

(5) (a) De Benneville. J. Org. Chem.. **6**, 462 (1941); (b) "Beilstein." **10**, 712; Simonis and Arand. Ber.. **42**, 3726 (1909); (c) Bromberg, Ber.. **29**, 1437 (1896); "Beilstein." **17**, 342.

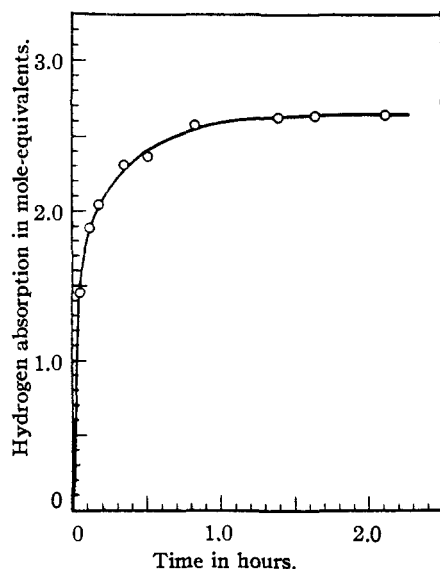(6) (a) Wojack. Ber.. **71**, 1102 (1938); (b) Koelsch and Byers. THIS JOURNAL. **62**, 560 (1940).

Fig. 1.—Catalytic hydrogenation of 0.158 mole of methyl α-isonitrosobutyrophenone-o-carboxylate.

After removal of the drying agent and the solvent, distillation of the residue gave a colorless product, b. p. 137–140° (4 mm.), $n^{20}D$ 1.5164–1.5190, in an 81–86% yield.

The 2,4-dinitrophenylhydrazone prepared from this ester was obtained as orange crystals after recrystallization from alcohol, cap. m. p. 143–145°.

Anal. Calcd. for $C_{12}H_{18}O_6N_4$: C, 55.95; H, 4.70; N, 14.50. Found: C, 55.95, 55.97; H, 4.79, 4.80; N, 14.77, 14.59.

Certain preparations of this ester underwent decomposition during distillation. The variation in physical and chemical properties is shown by 1–5 in Table I. Analyses of these ester preparations for propylidenephthalide by absorption spectra data and by quantitative catalytic hydrogenation on a semi-micro scale gave the results shown in the last two columns.

TABLE I

Ester no.	nD at T. °C.		Maximum yield of VI in the isonitroso reaction in %	Propylidene phthalide content in mole % by Abspn. spectra[a]	Cat. hydg.
1	1.5233	20	81	..	...
2	1.5309	19.7	77	24	23
3	1.5490	20	42	..	48
4	1.5510	19.7	41	51	51
5	1.5190	20	84	3	2
Propylidene-phthalide	1.586	20	..	..	104
6	1.5161	20.5	87	3	nil
7[b]	1.5171	20.5	55	4	nil

[a] Based on percentage transmission at 310 millimicrons. We are indebted to Mr. Albert Sample and Mrs. Josephine Butler for the data. [b] The acid precursor was prepared by Method A.

Preparation no. 5 differed from no. 4 only in that it was washed before distillation until it was completely free of acid.

It thus appeared that these preparations were mixtures of V, IX and/or III. In an effort to prepare the ester V in a pure state, the acid IV was treated with diazomethane to give ester no. 6. An attempt to prepare pure pseudo-

ester by the Fischer esterification method, using methyl alcohol and hydrogen chloride,[3] resulted in the product, no. 7, whose absorption spectra (Fig. 2, curve f) was unexpectedly found to be inappreciably different from that of ester no. 6 (Fig. 2, curve e).
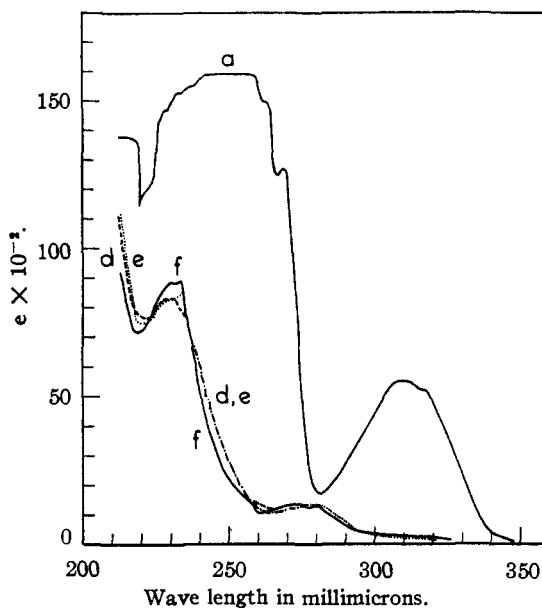

Fig. 2.—Absorption spectra: a, propylidenephthalide; d, ester no. 5, prepared from IV and methyl sulfate; e, ester No. 6 prepared from IV and diazomethane; f, ester No. 7, prepared from IV and methyl alcohol and hydrogen chloride.

Methyl α-Isonitrosobutyrophenone-o-carboxylate (VI, $R = -C_2H_5$).—The ester (V, R = $-C_2H_5$) (412 g., 2.0 moles) was dissolved in methylene chloride (1 liter) and treated at 5° successively with gaseous ethyl nitrite (3.0 moles in sixty minutes) and hydrogen chloride (3.0 moles in ninety minutes). One-half the solvent was removed by distillation, the residue was chilled, and the product was collected by filtration in 81–84% yield. Upon recrystallization from isopropanol (92% recovery), its corrected cap. m. p. was 150–151° with softening at 148°.

Anal. Calcd. for $C_{12}H_{13}O_4N$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.40, 61.75; H, 5.83, 5.62; N, 5.79, 5.98.

1-Amino-1-phthalidylpropane Hydrochloride, Isomer A (VIII, R = $-C_2H_5$).—The isonitroso compound (35 g., 0.158 m.) was dissolved in 95% alcohol (450 cc.). Twenty grams of previously used 10% palladinized charcoal catalyst and 42 cc. of concentrated hydrochloric acid were added. Hydrogenation was carried out in two hours at 30° at an initial hydrogen pressure of 500 lb./sq. in. The course of the hydrogen uptake was as shown in Fig. 1. The rapid absorption of two moles of hydrogen presumably indicates the formation of VII, half of which underwent slow reduction. After removal of the catalyst, the reaction mixture was taken to dryness *in vacuo*. The residue was collected and washed with acetone. ,The product, 1-amino-1-phthalidylpropane hydrochloride, isomer A, weighed 18.7 g., 55% yield, cap. m. p. 265–268° dec. (lit.[1] 268.5–270°). A sample was recrystallized from alcohol.

Anal. Calcd. for $C_{11}H_{14}O_2NCl$: Cl, 15.57. Found: Cl, 15.56, 15.56.

So far, the water-insoluble by-product of this reduction has not been identified.

Solvents other than 95% alcohol were tried, but all these—glacial acetic acid, or a mixture of dioxane and water to which three equivalents of concentrated hydrochloric acid per mole of compound reduced had been added, or absolute alcohol containing three equivalents of anhydrous hydrogen chloride as reduction media—gave considerably lower yields of amine salt. The yield was much lower when the amount of isonitroso compound reduced per given volume of solvent was greater than 35 g./450 cc., but a decrease in the amount reduced per given volume of solvent failed to increase the yield.

Methyl Propiophenone-o-carboxylate (V, R = CH₃).— o-Carboxypropiophenone, which was prepared by the methods used to prepare o-carboxybutyrophenone, was esterified in 87% yield; b. p. 137 (5 mm.) to 132° (4 mm.), n^{20}D 1.5260–1.5290 (lit.,[7] b. p. 157–158° (19 mm.), $n^{16.4}$D 1.5240).

Methyl α-Isonitrosopropiophenone-o-carboxylate (VI, R = CH₃).—This compound was recrystallized from methanol, m. p. 166–169° (Fisher block).

Anal. Calcd. for C₁₁H₁₁NO₄: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.84, 59.97; H, 4.93, 4.65; N, 6.33, 6.29.

1-Amino-1-phthalidylethane Hydrochloride, Isomer A (VIII, R = CH₃).—This compound was obtained in 64.9–74.5% yield and after recrystallization melted in the range 286–295° (lit.,[1] 292–296° dec.).

(7) Beilstein X-S. p. 334.

1-p-Nitrobenzoylamino-1-phthalidylethane (A) melted 188–189.5° after crystallization from alcohol (lit.[1] 188–189°).

Anal. Calcd. for C₁₇H₁₄O₅N₂: C, 62.57; H, 4.29; N, 8.58. Found: C, 62.47, 62.58; H, 4.29, 4.35; N, 8.54, 8.59.

Summary

1. A new synthesis of 1-amino-1-phthalidylalkanes has been reported.

2. This synthesis resulted in only one of the possible racemic forms of 1-amino-1-phthalidylethane and -propane.

3. In the preparation of the intermediate, methyl butyrophenone-o-carboxylate, the product underwent partial decomposition to propylidene-phthalide unless carefully freed of acid before distillation.

4. Observations have been reported on the relationship between normal and pseudo-esters of butyrophenone-o-carboxylic acid in regard to their ultraviolet absorption spectra and their ability to undergo the isonitroso reaction.

The Bitter Principles of Citrus Fruit.   I.   Isolation of Nomilin, a New Bitter Principle from the Seeds of Oranges and Lemons

BY OLIVER H. EMERSON

Limonin is a well recognized bitter principle in citrus plants that has been regarded as responsible for the bitter taste which sometimes appears in the juice of Navel oranges on standing or heating. Evidence which favors that view is presented here and points to a reaction whereby limonin may be formed from a precursor in orange juice. In addition a new bitter principle, "nomilin," has been isolated from the seeds of oranges and lemons. It appears closely related to limonin, and because of the similarity in properties it may also contribute to the bitter taste.

Limonin was first isolated by Bernay in 1841 and has since been obtained from a series of citrus and related *Rutaceae*,[1,2,3] having been found in the fleshy part of the fruit, the seeds, the bark and the roots. The chemical nature of the bitter principle has recently been discussed by Geissman and Tulagin.[4] It is well established that the substance is a dilactone of the formula C₂₆H₃₀O₈. It has no reactive hydroxyl groups, giving no methane with cold methylmagnesium iodide,[5] although Koller and Czerny reported it to give variable

(1) Schechter and Haller. THIS JOURNAL, **62**, 1307 (1940). This paper summarizes excellently the earlier literature.
(2) Mookerjee. *J. Indian Chem. Soc.*, **17**, 593 (1940).
(3) Seshadri and Veeraragavia, *Proc. Indian Acad. Sci.*, **11A**, 505 (1940).
(4) Geissman and Tulagin. *J. Org. Chem.*, **11**, 760 (1946).
(5) Koller and Czerny. *Monatsh.*, **67**, 248 (1936).

amounts when heated, which suggested to them the presence of a carbonyl group capable of enolization, although no carbonyl derivatives have been reported. No methoxyl or methylene dioxy groups have been detected, and the remaining three oxygen atoms are presumably present as cyclic ethers. Drastic treatment with potassium hydroxide yields 0.88 mole of acetone.[4]

The question of a carbonyl group, as postulated by Koller and Czerny, is obviously of importance to the problem of limonin. The absorption spectrum of limonin as measured by Geissman and Tulagin and in this Laboratory (Fig. 1) shows a weak band at about 290 mμ, log E = 1.4, which is suggestive of an isolated carbonyl group, though such a weak band could easily result from traces of an impurity. However, we have succeeded in preparing a beautifully crystalline oxime by treating limonin with hydroxylamine in the presence of pyridine, which will often permit the oximation of carbonyl groups that fail to react with hydroxylamine acetate.[6]

Isolimonin.—Besides limonin, Koller and Czerny[5] reported the isolation from orange seeds of an isomer of limonin melting at 258–259° which they called isolimonin. It crystallized from alcohol in thick "warty" crystals in contrast to the thin six-sided plates of limonin and differed from

(6) Bachmann and Boatner, THIS JOURNAL, **58**, 2097 (1936).