

In addition to bovine gamma globulin, we have reacted dinitrobenzene sulfonate with egg albumin, beef serum, sheep serum, gelatin and tuberculin with results similar to those given above.

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4-Nitro-2-thenaldehyde

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The nitration of 2-thenaldehyde diacetate has been reported to give 5-nitro-2-thenaldehyde diacetate.^{1,2} Since Rinkes³ found that nitration of methyl 2-thienyl ketone gave a mixture of methyl 5-nitro-2-thienyl ketone and methyl 4-nitro-2-thienyl ketone, it was thought that the nitration of 2-thenaldehyde diacetate should produce 4-nitro-2-thenaldehyde diacetate as well as the 5-nitro derivative. It was found that this was indeed the case. Concentration of the alcoholic filtrates from the recrystallization of the 5-nitro-2-thenaldehyde diacetate, m.p. 72–73°, yielded another nitrothenaldehyde diacetate, m.p. 54–55°. Acid hydrolysis of the latter gave the nitroaldehyde, m.p. 36–37°. Oxidation of the nitroaldehyde to the nitroacid, followed by esterification with methanol, gave a methyl ester, m.p. 99°, corresponding to the melting point of methyl 4-nitro-2-thiophenecarboxylate reported by Rinkes.⁴

Experimental

Since the conditions for the nitration of 2-thenaldehyde diacetate differ in some respects from the procedure used by Patrick and Emerson,¹ these differences are reported here.

To 143 g. of acetic anhydride at –5° was added, over a period of 17 minutes, 43.7 g. of fuming nitric acid (sp. gr. 1.5), the temperature being kept at –5 to 0°. A solution of 55 g. of 2-thenaldehyde diacetate in 102 g. of acetic anhydride was then added slowly, keeping the temperature a –5 to –10°. After addition was complete, the solution was stirred at 0° for three hours and then poured onto 1.0 kg. of ice. The mixture was allowed to stand for one hour and was then filtered. The precipitate was washed with a little cold water followed by cold alcohol and then dried, yielding 58.5 g., 88%, of the isomeric 5-nitro-2-thenaldehyde diacetates, m.p. 55–65°. Three recrystallizations from alcohol gave a 64% yield of 5-nitro-2-thenaldehyde diacetate,⁵ m.p. 68–69°.

4-Nitro-2-thenaldehyde Diacetate.—The combined alcoholic filtrates from the first two recrystallizations of the 5-nitro-2-thenaldehyde diacetate were evaporated to dryness. The residue was recrystallized from 18 cc. of alcohol, giving 5.2 g. of solid, m.p. about 50°. The 5.2 g. were recrystallized again from 7 cc. of alcohol, giving 4.0 g. of solid, m.p. 50–55°. A third recrystallization from 10 cc. of alcohol,

gave 3.7 g., m.p. 54–55°. Crystallization of a sample from petroleum ether did not further raise the melting point. The ultraviolet absorption maximum in water occurred at 2925 Å., E_M 6,300.

*Anal.*⁷ Calcd. for $C_9H_9NO_6S$: C, 41.70; H, 3.50; N, 5.40; S, 12.37. Found: C, 41.81; H, 3.37; N, 4.97; S, 12.31.

4-Nitro-2-thenaldehyde.—To a solution of 12.5 g. of sulfuric acid in 25 cc. of water was added 6.7 g. of 4-nitro-2-thenaldehyde diacetate. The mixture was refluxed in an atmosphere of nitrogen for 20 minutes, cooled and the resulting precipitate removed by filtration and then washed with cold water. It was recrystallized from a mixture of ether-petroleum ether to give 2.0 g., 50% of 4-nitro-2-thenaldehyde, m.p. 34–37°. Further recrystallization from petroleum ether raised the melting point to 36–37°. The ultraviolet absorption maximum in water occurred at 3025 Å., E_M 7,600.

Anal. Calcd. for $C_8H_7NO_5S$: C, 38.21; H, 1.92; N, 8.92; S, 20.40. Found: C, 37.74; H, 1.94; N, 8.95; S, 20.50.

The semicarbazone melted at 234–235°. A mixed melting point with the 5-nitro-2-thenaldehyde semicarbazone was depressed to 225–230°.

Anal. Calcd. for $C_8H_8N_4O_5S$: C, 33.64; H, 2.82; S, 14.97. Found: C, 33.87; H, 3.07; S, 14.69.

A similar hydrolytic procedure when applied to 5-nitro-2-thenaldehyde diacetate gave a 95% yield of 5-nitro-2-thenaldehyde,⁸ m.p. 70–72°.

Methyl 4-Nitro-2-thiophenecarboxylate.—To a suspension of 0.5 g. of 4-nitro-2-thenaldehyde in 3 cc. of 35% sulfuric acid was added dropwise a solution of 0.8 g. of sodium dichromate in 0.5 cc. of water, keeping the temperature below 40°. The mixture was stirred for 3 hours at room temperature and then kept at 0° for 15 hours. The precipitate was removed by filtration, washed with a little cold water, and then dried. It was dissolved in 5 cc. of methanol, 0.1 g. of sulfuric acid added and the solution refluxed for 3 hours. At the end of this time the solution was poured into 15 cc. of ice-water and sufficient sodium bicarbonate solution added to neutralize any excess acid. The solid which formed was removed by filtration and recrystallized twice from petroleum ether. The melting point was 98–99° (99°⁴).

Anal. Calcd. for $C_8H_7NO_4S$: S, 17.13. Found: S, 17.44.

(7) All the analyses were carried out by Mr. Joseph Corrado of these laboratories.

(8) The ultraviolet absorption maximum, in water, of an analytically pure sample occurred at 3150 Å., E_M 11,200.

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The Resolution of *p*-Ethylphenylmethylcarbinol. Infrared Spectra of Enantiomorphs and Racemates

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In connection with another problem we had occasion to resolve *p*-ethylphenylmethylcarbinol. The resolution was carried out by crystallization of the brucine and cinchonidine salts of the acid phthalate of the alcohol¹ and is described in detail in the experimental part. Melting point data of the active and racemic phthalates indicate that the racemic phthalate is a *dl*-compound.

Routine examination of the infrared spectra of the enantiomorphs and racemic phthalates revealed that while the (+)-, (–)- and racemic phthalates had identical spectra in chloroform solution—as was to be expected^{2a} the mull spectrum of the racemate (see Fig. 1) showed significant differences

(1) A. W. Ingersoll in R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 376.

- (1) T. Patrick and W. Emerson, *THIS JOURNAL*, **74**, 1356 (1952).
- (2) V. M. Zubarovskii, *Doklady Akad. Nauk S.S.S.R.*, **83**, 85 (1952); *C. A.*, **47**, 2166^a (1953).
- (3) I. Rinkes, *Rec. trav. chim.*, [4] **52**, 538 (1933).
- (4) I. Rinkes, *ibid.*, [4] **51**, 1134 (1932).
- (5) All melting points were taken on a Fisher-Johns apparatus and are corrected.
- (6) The ultraviolet absorption maximum, in water, of an analytically pure sample occurred at 3190 Å., E_M 8,300.

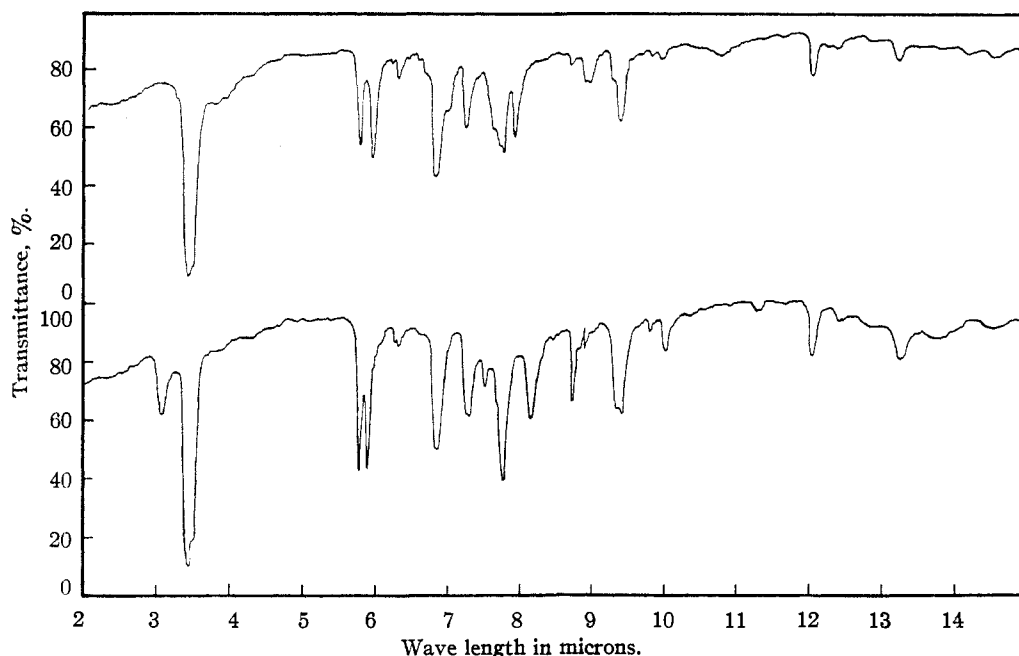


Fig. 1.—Infrared spectra of *p*-ethylphenylmethylcarbiny hydrogen phthalate in Nujol mull: upper curve, racemate; lower curve, enantiomorph.

from that of either enantiomorph, not only in the "fingerprint region" as expected,² but also in the 3–7 μ region of the infrared spectrum. Specifically, the enantiomorphs showed a sharp hydroxyl band at 3.05 μ and an acid carbonyl band at 5.88 μ in addition to the ester carbonyl band at 5.78 μ . The racemate had the same ester carbonyl band, but the hydroxyl band was absent and the acid carbonyl band was shifted to 5.95 μ . The precise fate of the hydroxyl band could be better observed in a hexachlorobutadiene mull (Fig. 2) where there was no interference from the 3.4–3.5 μ Nujol band. In this chlorinated mulling agent, the enantiomorphs showed sharp bands at 3.05 μ (OH) and 3.38–3.50 μ (CH) while the racemate showed a broad band at 3.4–3.6 μ with satellites at 3.79–3.97 μ , presumably due to combined OH- and CH-frequencies.

It is well known that both the hydroxyl band and the carbonyl band in carboxylic acids are shifted to longer wave lengths by hydrogen bonding.³ Thus one is led to the conclusion that *intermolecular* hydrogen bonding is much more important in the crystals of the racemic compound of *p*-ethylphenylmethylcarbiny phthalate than it is in the crystals of the enantiomorphs. One is tempted to conclude that the *dl*-compound is of the carboxylic acid dimer⁴ type while the enantiomorphs do *not* form such dimers in the solid state; but even if this is true, it is not general, since α -phenethyl phthalate does not show the shifts observed in the case of the

(2) (a) F. A. Miller in H. Gilman's "Organic Chemistry," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 136. (b) Results somewhat similar to those described here were reported by N. Wright. *J. Biol. Chem.*, **120**, 641 (1937); **127**, 137 (1939).

(3) (a) For a summary, see L. N. Ferguson, "Electron Structures of Organic Molecules," Prentice-Hall, Inc., New York, 1952, p. 262; (b) for recent references, see S. Searles, M. Tamres and G. M. Barrow, *THIS JOURNAL*, **75**, 71 (1953); P. A. Giguère and A. Weingartshofer Olmos, *Can. J. Chem.*, **30**, 821 (1952).

(4) Ref. 3a, p. 64.

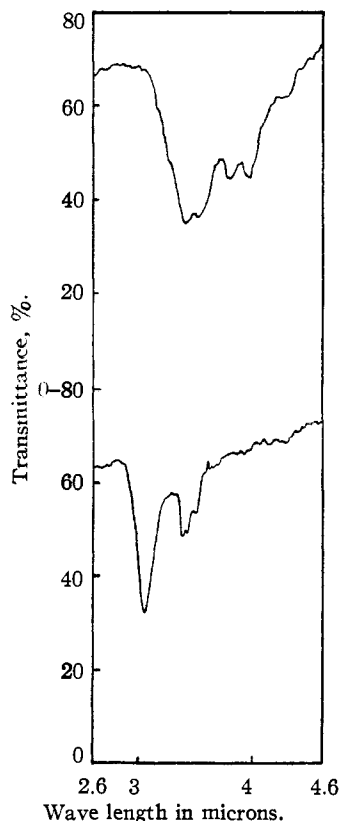


Fig. 2.—Infrared spectra of *p*-ethylphenylmethylcarbiny hydrogen phthalate in hexachlorobutadiene mull: upper curve, racemate; lower curve, enantiomorph.

p-ethyl homolog.⁵ It appears that in this case the

(5) α -Phenethyl phthalate also forms a racemic compound. The infrared spectra (Nujol mulls) of the racemate and of the enantiomorphs resemble that of the *dl*-compound of the *p*-ethyl homolog as well as that of methyl acid phthalate in that the hydroxyl band is absent and the acid carbonyl band is found at 5.95 μ .

d- and *l*-forms can dimerize with themselves as well as with each other.⁶ The apparent absence of dimerization of the enantiomorphs of the *p*-ethyl homolog must then be ascribed to steric interference of the ethyl groups. This steric interference appears to depend critically on the conformation of the molecules in the crystalline state and disappears in benzene or chloroform solution, in which both the enantiomorphs and the racemate of the *p*-ethylphenylmethylcarbonyl phthalate dimerize, as indicated by infrared spectra (absence of distinct OH-band) and molecular weight.

It would obviously be desirable to examine mull spectra of other racemates and enantiomorphs. We have had occasion to examine the infrared spectra of (+)- and *dl*-2-phenylpropanediol-1,2 and of (-) and *dl*-malic acid in hexachlorobutadiene. The OH-band for the racemic glycol⁷ lies at 3.16 μ while that for the enantiomorph is found at 3.08 μ , indicating the possibility of enhanced hydrogen bonding in the compound. In the spectra of the malic acids⁸ the principal difference appears in the resolved part of the OH-band which is a single sharp band at 2.9 μ in the racemate and a doublet at 2.84 and 2.98 μ in the active compound.

Experimental⁹

***dl*-*p*-Ethylphenylmethylcarbonyl Phthalate.**—A mixture of 165 g. (1.1 moles) of phthalic anhydride, 165 g. (1.1 moles) of the carbino¹⁰ (b.p. 111–113° (11–12 mm.),¹¹ n_D^{25} 1.5160,¹⁰ d_4^{25} 0.970¹¹; phenylurethan¹¹ m.p. 73–74°) and 87 g. (1.1 moles) of pyridine was heated for two hours on the steam-bath and then poured into an excess of dilute hydrochloric acid. The precipitated oil was extracted with ether and the ether layer was washed successively with dilute hydrochloric acid and water and then dried over sodium sulfate and concentrated. Crystallization of the residue from benzene-petroleum ether (b.p. 30–60°) yielded 287 g. (87%) of the phthalate, m.p. 82–84°. The analytical sample melted at 85–86°.

Anal. Calcd. for C₁₈H₁₈O₄: C, 72.47; H, 6.08; mol. wt. (dimer), 596. Found: C, 72.60; 6.37; mol. wt. (cryoscopically, in benzene), 545.

Resolution of *dl*-*p*-Ethylphenylmethylcarbonyl Phthalate.—To a solution of 135 g. (0.45 mole) of the *dl*-phthalate in 400 ml. of warm acetone was added 180 g. (0.45 mole) of brucine. On standing and chilling, a total of 170–190 g. of the crude brucine salt precipitated. This material was recrystallized three times from 300–400 ml. of acetone, care being taken to allow crystallization to take place slowly and without disturbance at room temperature. The recovered brucine salt weighed 62.5 g. (40%), melted at 113–114° (dec.) and had $[\alpha]_D^{25}$ -25.5° in 95% ethanol; the melting point and rotation were not changed by further recrystallization. The salt was decomposed by dissolving it in meth-

(6) The possibility of strong intramolecular hydrogen bonding in the case of α -phenethyl phthalate would offer an alternative explanation for the similarity in the spectra of the enantiomorphs and racemate. Some support for such an explanation comes from the position of the ester carbonyl band which occurs at 5.82 μ rather than at 5.78 μ as in the *p*-ethyl homolog. The position of the OH-band in the active forms of the *p*-ethyl compound (at 3.05 μ) suggests intramolecular hydrogen bonding also. The constancy of the ester C=O frequency and the marked shifts in the C—O (7.5–9 μ) region (see Fig. 1) in going from the racemate to the active form suggest that this hydrogen bonding may involve the alkyl oxygen of the ester group.

(7) E. L. Eliel and J. P. Freeman, THIS JOURNAL, 74, 923 (1952).

(8) We are indebted to Professor David Y. Curtin, University of Illinois (private communication) for drawing our attention to differences in the mull spectra of the malic and the tartaric acids.

(9) All melting and boiling points are uncorrected. Microanalysis by Micro-Tech Laboratories, Skokie, Ill.

(10) D. T. Mowry, M. Renoll and W. F. Huber, THIS JOURNAL, 68, 1105 (1946). The refractive index for *p*-ethylphenylmethylcarbonyl reported in this reference (1.5670 at 25°) appears to be misprinted.

(11) A. Klages, Ber., 35, 2245 (1902), reports b.p. 119.5° (14 mm.) d_4^{25} 0.974; phenylurethan m.p. 72–73°.

anol, pouring the solution into dilute hydrochloric acid and extracting the precipitated phthalate with ether. The ether solution was dried over sodium sulfate and concentrated and the residue crystallized from benzene-petroleum ether (30–60°) to give 23.1 g. (86%) of active phthalate, m.p. 108–109°, $[\alpha]_D^{25}$ +16.1° (α 1.125°, $l = 2$ dm., c 35 g./l., in absolute ether) unchanged by further recrystallization.

The crude (-)-phthalate recovered from the original acetone liquor was converted into the cinchonidine salt. To a solution of 48 g. (0.16 mole) of crude (-)-phthalate in 600 ml. of warm acetone was added 48 g. (0.16 mole) of cinchonidine. The solution was allowed to stand overnight and then chilled and the precipitated salt (65 g.) collected. After two recrystallizations from methanol-methyl acetate, the salt (28.5 g.) formed asbestos-like fibers melting at 173–174° (dec.) and had $[\alpha]_D^{25}$ -55.2°. The rotation was not increased by further recrystallization. Decomposition of 27 g. of the cinchonidine salt (in the same way as described for the brucine salt) yielded 12.2 g. (91%) of the active phthalate, m.p. 108–109°, $[\alpha]_D^{25}$ -16.3° (α -1.10, l 2 dm., c 33.8 g./l.). Recrystallization from benzene-petroleum ether (b.p. 30–60°) raised the melting point to 109.5–110.5° but the rotation was not increased; mol. wt. calcd. (dimer), 596; found (cryoscopically, in benzene), 541.

A mixture of equal amounts of the (+)- and (-)-phthalate upon crystallization from benzene-petroleum ether regenerated the racemate, m.p. 84–85°. When a mixture of the racemic modification and the (-)-form was melted, and the melt allowed to solidify, the melting point of the resulting solid was 82.5–86°. Similarly, the (+)-form depressed the melting point of the racemate (m.p. 85–86°) to 84–86°; on the other hand the melting point of the racemate was not affected in any way by simple melting and resolidification. These data indicate that the racemic modification is a compound.

The infrared spectra of the (+)-phthalate, (-)-phthalate and *dl*-phthalate were identical in chloroform solution, but mull spectra of the active forms in Nujol (Fig. 1) and hexachlorobutadiene (Fig. 2) differed from corresponding spectra of the racemate.

(+)- and (-)-*p*-Ethylphenylmethylcarbinol.—Hydrolysis of 9 g. of the (+)-phthalate was effected by heating for 15 minutes at 100° with 20 g. of a 20% solution of sodium hydroxide. The heterogeneous mixture was diluted with water, extracted with pentane, and the pentane extract dried over potassium carbonate and concentrated. Distillation of the residue gave 3.5 g. (78%) of active *p*-ethylphenylcarbinol, b.p. 117–118° (13 mm.), m.p. 13–15°, n_D^{25} 1.5159, d_4^{25} 0.970, α_D^{25} -90.31° (neat, $l = 2$ dm.); levorotation established by observing rotation of a dilute solution in the *dl*-alcohol whence $[\alpha]_D^{25}$ -46.5° (neat).

The (-)-phthalate similarly gave (+)-alcohol, b.p. 116–117° (12 mm.), m.p. 13–15°, n_D^{25} 1.5158, α_D^{25} +90.29° (neat, $l = 2$ dm.) whence $[\alpha]_D^{25}$ +46.5°.

When more dilute sodium hydroxide was used in the hydrolysis, the rotation of the resulting alcohol was the same indicating that alkyl-oxygen fission was apparently not taking place.¹²

Samples of (+), (-) and *dl*-alcohol all had the same infrared spectrum.

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(12) Cf. J. Kenyon, Bull. soc. chim. France, 66C (1951).

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β -(*p*-Nitrobenzoyl)-acrylic Acid and *p*-Nitroacrylophenone

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The antibacterial and antifungal activity reported for the α,β -unsaturated ketones, acrylo-