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*-ethylphenylmethylcarbinyl 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 glycol[7] lies at 3.16μ while that for the enantiomorph is found at 3.08μ, indicating the possibility of enhanced hydrogen bonding in the compound. In the spectra of the malic acids[8] the principal difference appears in the resolved part of the OH-band which is a single sharp band at 2.9μ in the racemate and a doublet at 2.84 and 2.98μ in the active compound.

Experimental[9]

***dl*-*p*-Ethylphenylmethylcarbinyl Phthalate.**—A mixture of 165 g. (1.1 moles) of phthalic anhydride, 165 g. (1.1 moles) of the carbinol[10] (b.p. 111–113° (11–12 mm.),[11] $n^{25}D$ 1.5160,[10] d^{25} 0.970[11]; phenylurethan[11] 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 $C_{18}H_{18}O_4$: 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*-Ethylphenylmethylcarbinyl 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 $[\alpha]^{25}D$ −25.5° in 95% ethanol; the melting point and rotation were not changed by further recrystallization. The salt was decomposed by dissolving it in methanol, 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°, $[\alpha]^{25}D$ +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 $[\alpha]^{27}D$ −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°, $[\alpha]^{25}D$ −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°, $n^{25}D$ 1.5159, d^{25} 0.970, $\alpha^{25}D$ −90.31° (neat, l = 2 dm.; levorotation established by observing rotation of a dilute solution in the *dl*-alcohol) whence $[\alpha]^{25}D$ −46.5° (neat).

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

Acknowledgment.—This work was supported by a Frederick Gardner Cottrell Grant of Research Corporation for which we are grateful. We are indebted to Mr. Thomas Marshall for the molecular weight determinations.

(6) The possibility of strong *intra*molecular 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 3.05μ) suggests *intra*molecular hydrogen bonding also. The constancy of the ester C=O frequency and the marked shifts in the C—O (7.5–9μ) 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*-ethylphenylmethylcarbinol 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^{18} 0.974; phenylurethan m.p. 72–73°.

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

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

BY HELEN F. GINSBERG, ILSE LEDERMAN AND DOMENICK PAPA

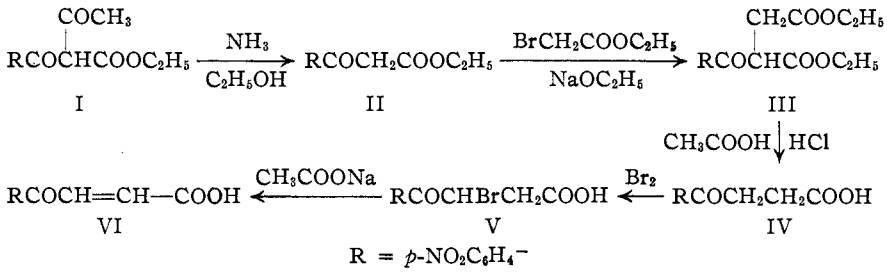
RECEIVED APRIL 27, 1953

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

phenones and β-aroylacrylic acids,[1] indicates that these substances are of potential clinical interest. In general, aromatic substitution by chlorine, methyl and hydroxyl groups enhanced the activity of these two types of compounds.

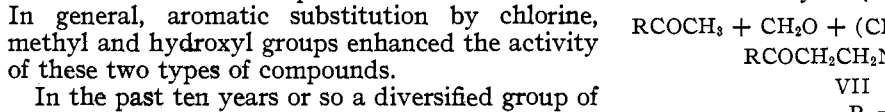
In the past ten years or so a diversified group of chemotherapeutic agents have been described, several of these substances having in common an "aryl" nitro group.[2] It therefore was of interest to prepare the *p*-nitro analogs of β-benzoylacrylic acid and acrylophenone in order to determine whether substantial enhancement of the antibacterial and/or antifungal activity would result by this substitution. Although β-(*m*-nitrobenzoyl)-acrylic acid, prepared in the course of a previous study,[1] was less active than the parent compound, it was reasonable to assume that the para isomer would be appreciably more active, *cf.*, sulfa drugs, chloramphenicol, etc.

The position of the substituents in the proposed compounds precluded direct nitration of the easily available intermediates. β-(*p*-Nitrobenzoyl)-acrylic acid was prepared by the sequence of reactions described by Kotake, *et al.*,[3] for the synthesis of β-(2-nitro-3-methoxy)-acrylic acid.



The reaction of freshly prepared *p*-nitrobenzoyl chloride with ethyl acetoacetate in absolute ethanol gave I in good yield. Substitution of commercial *p*-nitrobenzoyl chloride in the condensation afforded ethyl *p*-nitrobenzoylacetate (II) identical with that obtained from the ethanolic ammonia hydrolysis of I. Alkylation of II with ethyl bromoacetate followed by acid hydrolysis of the crude diester (III) gave *p*-nitrobenzoylpropionic acid (IV). Bromination of IV in chloroform[4] and subsequent dehydrohalogenation of the bromoketonic acid (V) with sodium acetate yielded the β-nitrobenzoyl)-acrylic acid (VI).[5]

Attempts to prepare *p*-nitroacrylophenone by adapting procedures applicable to the ortho and meta isomers were unsuccessful. Although both *o*- and *m*-nitroacetophenone have been reported to undergo the Mannich condensation with amines and formaldehyde[6] (VII), there is no record of the



use of the *p*-nitro compound in this reaction. The desired Mannich bases were obtained from the reaction of *p*-nitroacetophenone, formaldehyde and a secondary amine hydrochloride in ethanol solution; however, the yields were consistently low and unreliable. In one run the product from piperidine hydrochloride was isolated; yet the experiment could not be successfully repeated. The only consistent results in this condensation were obtained with dimethylamine hydrochloride. Several attempts to decompose *p*-nitro-ω-dimethylaminopropiophenone hydrochloride to the acrylophenone (VIII), such as by treatment with alkali or steam distillation, resulted in either polymerization or formation of intractable oils. In view of these difficulties and the relatively low order of activity of the β-(*p*-nitrobenzoyl)-acrylic acid, these reactions were not studied further.

Experimental

Ethyl α-(*p*-nitrobenzoyl)-acetoacetate (I) from 33.4 g. of *p*-nitrobenzoic acid through the acid chloride and subsequent condensation with ethyl acetoacetate as described,[3] yield 35 g., m.p. 55–56° after recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{13}O_6N$: C, 55.91; H, 4.69. Found: C, 55.45; H, 5.06.

In the initial preparation of this compound, commercial *p*-nitrobenzoyl chloride gave ethyl *p*-nitrobenzoylacetate, m.p. 73–74°, identical with that obtained in the ethanolic ammonia hydrolysis of I.

Ethyl 4-nitrobenzoylacetate (II) from I (25 g.) and ethanolic ammonia, yield 17 g., m.p. 73–74° after recrystallization from ethanol.

Anal. Calcd. for $C_{11}H_{11}O_5N$: N, 5.91. Found: N, 5.93.

β-(4-Nitrobenzoyl)-propionic Acid (IV).—The intermediate diethyl-α-(*p*-nitrobenzoyl) succinate prepared from II (20.5 g.) and ethyl bromoacetate was obtained as a pale yellow oil and hydrolyzed directly with mixed acetic and hydrochloric acids, yield 16 g., m.p. 150–151° after recrystallization from water.

Anal. Calcd. for $C_{10}H_9O_5N$: C, 53.81; H, 4.07. Found: C, 53.38; H, 4.13.

β-Bromo-β-(4-nitrobenzoyl)-propionic Acid (V).—The bromination of IV was carried out as described for a series of aroylpropionic acids.[4] From 5 g. of III, there was obtained 6.5 g. of the bromo acid, m.p. 118–119.5° after recrystallization from benzene–petroleum ether.

Anal. Calcd. for $C_{10}H_8O_5NBr$: N, 4.63. Found: N, 4.89.

β-(*p*-Nitrobenzoyl)-acrylic Acid (VI).—Dehydrohalogenation of the bromo acid (V) (4.6 g.) with acetic acid and sodium acetate gave the acrylic acid, yield 2.5 g., m.p. 173.5–174.5° after recrystallization from water.

Anal. Calcd. for $C_{10}H_7O_5N$: C, 54.30; H, 3.19; N, 6.33. Found: C, 54.38; H, 3.23; N, 6.18.

***p*-Nitro-ω-piperidinopropiophenone Hydrochloride.**—*p*-Nitroacetophenone (16.5 g.) was added gradually in one-half hour to a refluxing solution of 12.2 g. of freshly prepared piperidine hydrochloride and 4.5 g. of paraformaldehyde in

(1) See references 2–5, D. Papa, E. Schwenk, F. Villani and E. Klingsberg, THIS JOURNAL, **70**, 3356 (1948).

(2) Nisulfadine and Nisulfazole, R. H. Major and H. L. Douglas, *J. Kansas Med. Soc.*, **43**, 287 (1942); R. H. Major, *Am. J. Med.*, **1**, 484 (1946). Derivatives of nitrobenzene and nitrofuran, M. D. Eaton, C. T. Huang and C. G. Levenson, *Proc. Soc. Exptl. Biol. Med.*, **71**, 501 (1949); M. C. Dodd, D. L. Cramer and W. C. Ward, *J. Am. Pharm. Assoc., Sci. Ed.*, **39**, 313 (1950); M. C. Rebstock, G. W. Moersch, A. C. Moore and J. M. Vandenbelt, THIS JOURNAL, **73**, 3666 (1951); and others.

(3) M. Kotake, T. Saken and S. Senoh, THIS JOURNAL, **73**, 1832 (1951).

(4) E. B. Knott, *J. Chem. Soc.*, 455 (1945).

(5) Recently M. Goldman and E. I. Becker, *Nature*, **170**, 35 (1952), described a procedure for the preparation of aroylacrylic acids applicable to compounds containing a negative substituent such as the *p*-nitro group.

(6) (a) C. Mannich and M. Dannehl, *Arch. Pharm.*, **276**, 206 (1938); (b) H. Jager and M. Arens, *Chem. Ber.*, **83**, 152 (1950).

30 cc. of 2B ethanol. Then an additional 3 g. of paraformaldehyde was added, the reaction mixture refluxed for 15 minutes and filtered hot. The product separated from the cooled filtrate, yield 4 g., m.p. 193–194° after recrystallization from ethanol–acetone.

Anal. Calcd. for $C_{14}H_{19}O_3N_2Cl$: N, 9.38. Found: N, 9.64.

p-Nitro-ω-dimethylaminopropiophenone Hydrochloride.—To a refluxing solution of 40.75 g. of dimethylamine hydrochloride, 22.5 g. of paraformaldehyde, 1.5 cc. of concentrated hydrochloric acid in 200 cc. of 2B ethanol, 82.5 g. of *p*-nitroacetophenone was added portionwise over a period of 1 hour. The reaction mixture was refluxed an additional 15 minutes, cooled and the keto base filtered, yield 20 g., m.p. 190–191° after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{11}H_{15}O_3N_2Cl$: N, 10.83. Found: N, 10.86.

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Some Notes on the Chemistry of Arsafluorinic Acid[1]

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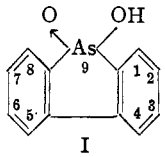
Arsafluorinic acid (I) has been the object of only scant attention. Aeschlimann, *et al.*,[2] were the first to report its preparation from ring closure of biphenyl-2-arsonic acid.



I

The chemistry of the system was somewhat extended by Cookson and Mann[3] who prepared several 9-substituted arsafluorenes. Recently, Feitelson and Petrow[4] reported a more varied series of compounds obtained by ring-closure methods and by direct substitution. This last publication appeared when we were in the final stages of some research in the same field. Though our efforts were not so extensive as those of Feitelson and Petrow, many of the compounds reported by them had been prepared by us, and agreement on the data concerning these was, in general, very good. There were some points of difference, however, and some new material which may be of interest in view of the paucity of information pertaining to the system.

The parent compound, arsafluorinic acid, was synthesized according to the method of Aeschlimann by treating biphenyl-2-arsonic acid with concentrated sulfuric acid for ten minutes at 100°. The compound obtained, however, had consistently a melting point of 327–328°. Since Cookson and Mann had reported a melting point of 299°, the product was submitted to further examination. Conversion to 9-chloro- and 9-iodoarsafluorene gave products melting at described temperatures.[2] The neutral equivalent, determined by titration with standard alkali in an alcohol–water medium using phenolphthalein indicator, gave values (260, 259) close to the calculated molecular weight of the compound. Arsenic analysis gave results consistent with the calculated content. Finally, hydrolysis and oxidation of 9-chloroarsafluorene by addition of 30% hydrogen peroxide to the suspension of the compound in hot potassium hydroxide solution gave, on acidification, arsafluorinic acid melting at 328–328.2°. The purity of the compound was then confirmed. Feitelson and Petrow indicate the melting temperature to be above 300°.

A simpler method for preparing the 9-chloro derivative was discovered. It consists in suspending arsafluorinic acid in glacial acetic acid, heating to 80° and adding phosphorus trichloride dropwise with stirring until the arsinic acid dissolves. Cooling effects the separation of 9-chloroarsafluorene in good yield and purity. This procedure was also applied, using chloroform as a solvent and phosphorus tribromide, to prepare for the first time 9-bromoarsafluorene, melting at 178°. Nitration of arsafluorinic acid to give the 2-nitro compound was accomplished by a method very similar to that described by Feitelson and Petrow,[4] but these authors do not comment on the surprising ease of nitration. The reaction is carried out at 5° with little more than the calculated quantity of nitric acid. This facility for nitration is unexpected in view of the electronegativity of the arsinic acid grouping. Dinitration is imminent and is, indeed, readily accomplished under mild conditions.

From the nitroarsinic acid, 2-nitro-9-chloroarsafluorene was prepared by the action of phosphorus trichloride. These haloarsines are useful compounds for purification and characterization since they represent soluble, crystallizable materials with good melting points. In the same way, 3-nitroarsafluorinic acid, obtained by ring closure of 5-nitrobiphenyl-2-arsonic acid, was converted to 3-nitro-9-chloroarsafluorene. Similarly, in the case of intermediates used in ring closing attempts, 5-nitrobiphenyl-2-dichloroarsine and 4′-nitrobiphenyl-2-dichloroarsine were prepared.

Reduction of the 2-nitro compound to the amine was accomplished with alkaline ferrous hydroxide in a manner similar to that already described[4] except that boiling-water temperature was used in the final stage. This amine decomposed without melting and had a clean yellow color instead of the pink color described for it. We suggest that the pink color of the material obtained by Feitelson and Petrow was due to the presence of some dinitroarsafluorinic acid in the starting material since we have obtained a light red product from attempts to reduce the dinitro compound with hot alkaline ferrous hydroxide. In the latter case evidence is incomplete, but our observations are at variance with those of Feitelson and Petrow who claim to have been unable to effect reduction of the dinitro-arsinic acid either with ferrous hydroxide or catalytic hydrogenation. Our light red material is probably not the diamine, but represents at least a partially reduced stage, perhaps the nitroamine.

Experimental

Preparation of Haloarsines. General Procedure.—Approximately 2 g. of the arsonic or arsinic acid was suspended

(1) Abstracted from a thesis presented by I. Victor Mattei in partial fulfillment of the requirements for the Master of Science degree at Xavier University.

(2) J. A. Aeschlimann, N. D. Lees, N. P. McLeland and G. N. Nicklin, *J. Chem. Soc.*, **127**, 66 (1925).

(3) G. H. Cookson and F. G. Mann, *ibid.*, 2888 (1949).

(4) B. N. Feitelson and V. Petrow, *ibid.*, 2279 (1951).