[CONTRIBUTION NO. 1592 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

6-Nitrocinchophen and Related Substances[1]

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The synthesis of 6-nitrocinchophen by two methods has been accomplished and a reported synthesis is shown to be in error. Although the orthodox Pfitzinger condensation and Doebner reaction both fail to give this acid, it may be prepared by suitable modification of these procedures.

In connection with another investigation[3] it became desirable to study the preparation of 6-nitrocinchophen (I). The literature dealing with this topic is limited to a claimed synthesis[4] of I, isolated as the insoluble potassium salt from the Pfitzinger reaction carried out with 5-nitroisatin (II), acetophenone and alkali. Borsche[5] had previously found that *p*-nitroaniline (III), pyruvic acid and benzaldehyde, under the standard conditions for the Doebner reaction did not yield I.

A reinvestigation of the Pfitzinger method disclosed that it proceeded abnormally. There was formed a variety of products among which were identified the azoxy acid (IV) (the supposed I of the earlier workers[4]), easily isolated as its insoluble potassium salt, and the amino acid (V). IV was converted by way of the acid chloride to the diester (IVa) which, on catalytic reduction, took up two molecular equivalents of hydrogen to yield the hydrazo compound. On reduction[4] with stannous chloride and hydrochloric acid, IV was smoothly converted to V. The previously reported[4] preparation of V (from IV, the supposed I) is therefore valid.

Since the above course of the Pfitzinger reaction is the result of the lability[6] of the nitro group in the presence of alkali, a method of the Knoevenagel type recommended by Lindwall[7] for use with sensitive isatins was tried but no hydroxyphenacyloxindole was formed from II under the Lindwall conditions.[8] However a patented process[9] originally applied to isatin and more recently[10] for the preparation of 2,3-dimethyl-6-nitrocinchoninamide from II was successful. When II was heated under pressure with acetophenone and aqueous ammonia it was converted to the amide (VI) which on hydrolysis with sulfuric acid gave I (isolated as the ester (Ia)).

In view of the discovery[3] in this Laboratory that 8-nitrocinchophen is easily prepared by a modified Doebner reaction, a study was made of the employment of this procedure for obtaining I. The modified Doebner with III (concentrated sulfuric acid was added to the reactants in glacial acetic acid), although successful, was less satisfactory than with *o*-nitroaniline. However, taking into account the availability of starting materials and operational ease, this synthesis must be considered superior to the preparation of I from II.

Catalytic reduction of the almost colorless nitro ester (Ia) gave rise to an orange (or yellow) colored[11] amino ester (Va) identical with the product of esterification of V (from the Pfitzinger directly, from reduction of IV, or from *p*-aminoacetanilide *via* the Doebner reaction[12]).

Experimental[13]

Pfitzinger Condensation.—Following the previously described[4b] procedure there was isolated from 38.4 g. of II[14] 22.2 g. of insoluble potassium salt as yellow needles. Material from a like experiment was recrystallized from 600 ml. of water–ethanol (2:1) with the aid of charcoal; yield 18.5 g. The analysis (recrystallized analytical sample gave λ_{max} 264, 373–375 mμ) indicated a hydrated salt of 6,6′-azoxycinchophen (IV).

Anal. Calcd. for $C_{32}H_{18}K_2N_4O_5 \cdot 4H_2O$: C, 55.80; H, 3.81; K, 11.35; N, 8.13. Found: C, 55.69, 55.72; H, 3.98, 3.97; K, 11.31, 11.44; N, 8.21, 8.06.

The filtrate from the 22.2 g. of salt was added to 3 l. of strongly acid ice-water. After separation of the resulting precipitate, the solution was neutralized to congo red whereupon a gelatinous precipitate formed which soon crystallized and was filtered off. This material (18 g.) was refluxed with 900 ml. of 30% ethanol; the solution, after filtering from amorphous matter, deposited 6-aminocinchophen (V)[15] as red needles; yield 11.1 g. In agreement with the

(1) The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology; responsible investigator, Dr. E. R. Buchman.

(2) Office of Naval Research, Pasadena, California.

(3) E. R. Buchman, C. M. McCloskey and J. A. Seneker, THIS JOURNAL, **69**, 380 (1947).

(4) (a) Meister Lucius and Brüning, German Patent 287,804 (Friedlaender, *Fortschr. Teerfarbenfabrikation*, **12**, 725; *Chem. Zentr.*, **86**, II, 1062 (1915)); (b) H. O. Calvery, C. R. Noller and R. Adams, THIS JOURNAL, **47**, 3058 (1925).

(5) W. Borsche, *Ber.*, **41**, 3884 (1908).

(6) *Cf.* production of azoxybenzene and aniline by the action of alcoholic potassium hydroxide on nitrobenzene, "Beilstein," 4th Ed., Vol. XVI, p. 621.

(7) R. N. Du Puis and H. G. Lindwall, THIS JOURNAL, **56**, 471 (1934).

(8) H. G. Lindwall and J. S. Maclennan, *ibid.*, **54**, 4739 (1932).

(9) Bayer and Co., German Patent 290,703 (Friedlaender, *Fortschr. Teerfarbenfabrikation*, **12**, 724; *Chem. Zentr.*, **87**, I, 645 (1916)).

(10) V. A. Petrow, *J. Chem. Soc.*, 18 (1945); *cf.* also ref. 3.

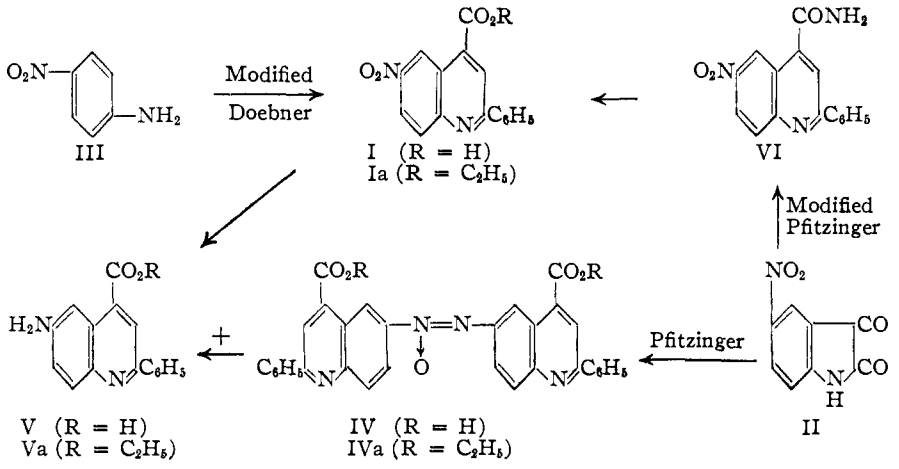
(11) It had been noted[3] that reduction of nearly colorless 8-nitrocinchoninic esters yielded highly colored 8-amino esters.

(12) (a) Schering, German Patent 287,216 (Friedlaender, *Fortschr; Teerfarbenfabrikation*, **12**, 713; *Chem. Zentr.*, **86**, II, 933 (1915)). (b) Meister Lucius and Brüning, German Patent 294,159 (Friedlaender, *Fortschr. Teerfarbenfabrikation*, **13**, 824; *Chem. Zentr.*, **87**, II, 707 (1916)).

(13) All melting points are corrected; microanalyses by Dr. G. Oppenheimer and staff of this Institute, by Huffman Microanalytical Laboratories, Denver, Colorado, and by Dr. A. Elek, Los Angeles; spectrophotometry by Mrs. B. Dandliker. The solvent used in the spectrophotometry was ethanol. Detailed spectra of the substances for which spectra data are given below can be obtained by ordering Document 3666 from American Documentation Institute, 1719 N Street, N. W., Washington 6, D. C., remitting $1.00 for microfilm (images 1 inch high on standard 35 mm. motion picture film) or $1.00 for photocopies (6 × 8 inches) readable without optical aid.

(14) See W. C. Sumpter, *Chem. Revs.*, **34**, 405 (1944); H. Rupe, *Helv. Chim. Acta*, **19**, 1315 footnote (1936). II exhibited λ_{max} at 331 mμ; *cf.* A. Korczynski and L. Marchlewski, *Ber.*, **35**, 4337 (1902).

(15) Authentic V was prepared[12b] from 15 g. of *p*-aminoacetanilide. Satisfactory results were obtained when this reagent was allowed to react first with benzaldehyde, the resulting Schiff base crystallizing from the boiling ethanolic solution; anhydrous pyruvic acid was then added and on continued refluxing the solid went into solution and 6-acetamidocinchophen started to come out. This latter (crude 11.2 g.) yielded 7.5 g. of V. Absorption maxima were found at 280, 404 mμ; however the solutions of V proved unstable, *cf.* 8-aminocinchoninic acid,[3] and the 404 mμ peak shifted with time to shorter wave lengths.



literature[4a,b,12a,b] an analytical sample, similarly recrystallized, melted with decomposition *ca.* 257°; when a capillary containing the material was inserted into a bath at 230°, the substance melted and then resolidified.

Anal. Calcd. for $C_{16}H_{12}N_2O_2 \cdot 1.5H_2O$: C, 65.97; H, 5.19. Found: C, 66.40, 65.99[16]; H, 4.92, 5.30.[16]

Hydrated V, after drying at 135°, gave analytical figures agreeing with $C_{16}H_{12}N_2O_2$ (Calcd.: N, 10.60. Found: N, 10.63.) Regarding conversion to the ester (Va) see below.

Diethyl 2,2'-Diphenyl-6,6'-azoxycinchoninate (IVa).—The acid (IV)[4b] (very difficultly soluble in solvents other than concentrated sulfuric acid) could not be esterified by refluxing with ethanolic sulfuric acid. Five grams of IV was refluxed with 30 ml. of thionyl chloride for three hours. Excess thionyl chloride was distilled from the resulting solution and the residue was refluxed for two hours with 30 ml. of ethanol containing a little anhydrous pyridine. The mixture was cooled to room temperature and the solid was filtered off and recrystallized from pyridine, yield 5 g. of fine yellow needles. IVa was recrystallized from nitrobenzene and from acetic acid, m.p. 217.5–218°; for analysis a portion was crystallized from *n*-butanol.

Anal. Calcd. for $C_{36}H_{28}N_4O_5$: C, 72.47; H, 4.73; N, 9.39. Found: C, 72.48, 72.38; H, 4.77, 4.80; N, 9.36.

Diethyl 2,2'-Diphenyl-6,6'-hydrazocinchoninate.—One gram (0.00168 mole) of IVa was dissolved in 200 ml. of hot ethylene glycol monomethyl ether and the solution cooled to 40°. Reduced catalyst (from 0.2 g. of platinum oxide) was added together with 25 ml. of the same solvent and the mixture was shaken in a hydrogen atmosphere for 30 minutes; about 0.0036 mole of hydrogen was absorbed. After filtration and cooling to 0°, the product crystallized, yield 0.6 g.; a second crop, 0.36 g., was obtained. The hydrazo ester crystallized from ethylene glycol dimethyl ether in red needles, m.p. 262.5–263°.

Anal. Calcd. for $C_{36}H_{30}N_4O_4$: C, 74.21; H, 5.19; N, 9.62. Found: C, 74.20, 74.17; H, 4.95, 5.01; N, 9.45, 9.53.

Modified Pfitzinger.[9,10]—A mixture of 15.6 g. of II, 18 ml. of acetophenone and 80 ml. of concentrated ammonium hydroxide was shaken in an autoclave for nine hours at 130°. The autoclave was cooled, the aqueous phase was separated by decantation and the residue was washed with 750 ml. of ethanol to remove tar. The remaining insoluble material was recrystallized from 200 ml. of nitrobenzene, yielding 3.77 g. (15.8%) of 2-phenyl-6-nitrocinchoninamide (VI) as faintly-yellow, fine needles, m.p. 295–295.5°, λ_{max} 245, 336–7 mμ.

Anal. Calcd. for $C_{16}H_{11}N_3O_3$: C, 65.52; H, 3.78; N, 14.33. Found: C, 65.79; H, 3.96; N, 14.16.

One-half gram of VI in 2 ml. of concentrated sulfuric acid was heated at 145° for three hours; the solution was then added to 20 ml. of ethanol and refluxing was continued for four hours. The reaction mixture was poured into ice-water and made basic with ammonia; the precipitate was recrystallized from butanone, yield 0.3 g. (55%) of ethyl 2-phenyl-6-nitrocinchoninate (Ia), m.p. 146.5–147°, identical (mixed m.p.) with material obtained from the Doebner reaction (see below).

Modified Doebner.[3]—Into a 250-ml. flask was placed 17.25 g. (0.125 mole) of finely powdered *p*-nitroaniline (III) and 12.5 ml. of glacial acetic acid; a mixture of 13.25 g. (0.125 mole) of benzaldehyde and 11 g. (0.125 mole) of anhydrous pyruvic acid was then added followed immediately by 11 ml. of concentrated sulfuric acid. The flask was swirled to ensure mixing; an exothermic reaction took place leading to the formation of a homogeneous solution. After standing for 30 minutes, 150 ml. of chloroform was added followed by 250 ml. of water and 50 ml. of concentrated aqueous ammonia. The mixture was well agitated and filtered and the insoluble material was again extracted by shaking with 50 ml. of chloroform and 300 ml. of water containing a trace of ammonia. The combined chloroform phases were re-extracted with 500 ml. of water containing ammonia and ammonium chloride and this extract was added to the combined aqueous ammoniacal phases. Acidification of the latter with concentrated hydrochloric acid led to precipitation of crude I which, after standing, was filtered off, dried and esterified by refluxing for five hours with 40 ml. of ethanol containing 6 ml. of concentrated sulfuric acid. After standing overnight, the ester (2.69 g.) had crystallized out; including material (0.2 g.) obtained by reworking the mother liquors, the yield was 7.2%. Ia was recrystallized from butanone, light yellow needles, m.p. 146–147°, λ_{max} 248, 276–278, 346 mμ.

Anal. Calcd. for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.13; H, 4.41; N, 8.54.

Varying the proportion of or the order of addition of the reactants did not significantly improve the yield. Saponification of Ia by boiling for a short time with aqueous alcoholic sodium hydroxide gave, on cooling, a crystalline sodium salt which was filtered off and converted to the free acid. I was recrystallized from glacial acetic acid (prisms) and from ethanol (needles), m.p. 234–234.5° (not entirely reproducible).

Anal. Calcd. for $C_{16}H_{10}N_2O_4$: C, 65.30; H, 3.43. Found: C, 65.28, H, 3.85.

Ethyl 2-Phenyl-6-aminocinchoninate (Va).—A mixture of Ia (2 g.), 0.2 g. of platinum oxide and 100 ml. of methanol, absorbed three molecular equivalents of hydrogen on shaking in a hydrogen atmosphere for 30 minutes. After filtering from catalyst and removing solvent by distillation, the residue was extracted by refluxing with 100 ml. of ligroin (60–70°). On cooling, the extract deposited a yellow crystalline solid, which, after further recrystallization melted at 109.3–109.8°, yield 0.2 g. (11%); the poor yield was due to the readiness with which the aminoester reacted with itself. Va crystallized from hot ligroin in the form of small orange prisms, from cold ligroin as yellow needles, λ_{max} 283, 410–412 mμ, strong light green fluorescence in ultraviolet light.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.20; H, 5.41; N, 9.91.

Two grams of V (from reduction[4] of IV potassium salt) was esterified by refluxing for five hours with 40 ml. of ethanol containing 4 ml. of concentrated sulfuric acid. The reaction mixture was poured into ice-water, the solution was made basic, and the precipitated solid was dried and extracted with 250 ml. of ligroin–isopropyl ether (6:1). Va crystallized on cooling and a second crop was obtained from the mother liquors; total yield 1.42 g. (64%), m.p. 109–109.5° from isopropyl ether, m.p. unchanged when mixed with material from Ia. Other samples of V (from the Pfitzinger condensation directly or from *p*-aminoacetanilide[15]), on esterification, gave similar results. All Va preparations were further characterized by conversion (with benzoyl chloride in the presence of pyridine) to ethyl 2-

(16) This set of analytical figures was secured on a sample of V prepared by reduction[4a,b] of IV potassium salt and recrystallized from aqueous ethanol.

phenyl-6-benzamidocinchoninate, colorless needles, m.p. 177–177.5° from ethanol, λ_{max} 280–281, 363–367 mμ, strong blue fluorescence under ultraviolet light.

Anal. Calcd. for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.09; N, 7.07. Found: C, 75.75; H, 5.17; N, 7.22.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Preparation of Organolead Compounds Containing Water-solubilizing Groups

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A number of new organolead compounds of the type $(C_6H_5)_3PbR'$ were prepared from triphenyllead–lithium and alkyl halides. The R′ part was chosen such that it would contain functional groups conceivably capable of conversion into water-solubilizing structures. Triphenyl-*p*-bromobenzyllead did not react to form a Grignard reagent or organolithium compound. Triphenyl-ω-haloalkylleads could not be obtained in pure form by reaction of excess α,ω-dihaloalkane with triphenyllead–lithium. When the latter reagent was in excess, however, α,ω-bis-(triphenyllead)-alkanes were readily obtained. Triphenyl-γ-diethylminopropyllead was prepared from triphenyllead–lithium and γ-diethylaminopropyl chloride. It was cleaved by dilute aqueous hydrochloric acid to give crystalline diphenyl-γ-diethylaminopropyllead chloride hydrochloride. Some lead compounds containing tertiary amino groups were converted to quaternary ammonium iodides or methyl sulfate derivatives to give products sufficiently soluble for physiological testing. One of these, the methyl sulfate derivative of triphenyl-γ-diethylaminopropyllead, was extremely soluble in water.

In a study recently reported[2] from this Laboratory, it was shown that organolead compounds of the type R_3PbR' could be obtained in good yields by the reaction of triaryllead–lithium preparations with alkyl halides. The triaryllead–lithium component was formed by treatment of one mole of lead dichloride, at −10°, with three equivalents of the aryllithium compound in ether.

$$3RLi + PbCl_2 \longrightarrow R_3PbLi + 2LiCl$$
$$R_3PbLi + R'X \longrightarrow R_3PbR' + LiX$$

In these equations R = aryl and X = halogen. Investigation of these reactions led to the conclusion that the method should be generally applicable for R_3PbR' compounds in which R′ is an aliphatic structure containing no functional group which will react rapidly with aryllithium compounds. This latter requirement was due to the fact that the triaryllead–lithium preparations were found to behave as an equilibrium system containing RLi as well as R_3PbLi.

$$R_3PbLi \rightleftharpoons R_2Pb + RLi$$

The present paper reports the application of this synthetic procedure to the preparation of some new organolead compounds of the type R_3PbR', where R′ contained functions conceivably capable of modification to produce water-solubilizing groups. The importance of this latter consideration for pharmacological evaluation has been discussed previously.[3] The compounds whose synthesis is described here include two water-soluble organolead derivatives which have been submitted for pharmacological testing elsewhere.

Halogen Compounds.—Of the structures allowable in the R′ group the most promising for our purposes appeared to be halogen atoms (which might be converted to other functions *via* the Grignard reaction) or tertiary amino groups. From triphenyllead–lithium and *p*-bromobenzyl chloride, triphenyl-*p*-bromobenzyllead was readily prepared. Attempts to form a Grignard reagent or organolithium compound from the triphenyl-*p*-bromobenzyllead did not succeed, however. In the only reported case[4] of unambiguous formation of a Grignard reagent from an organolead compound (triethyl-ε-bromoamyllead) the halogen atom was attached to an aliphatic carbon atom. Attempts were therefore made to obtain lead compounds containing a haloalkyl group by treatment of triphenyllead–lithium with excess polymethylene dihalide.

$$(C_6H_5)_3PbLi + X(CH_2)_nY \longrightarrow (C_6H_5)_3Pb(CH_2)_nY + LiX$$

(In this equation, X and Y are halogen atoms, which may or may not be of the same kind.) With an excess of a reagent such as trimethylene chlorobromide, triphenyllead–lithium reacted readily, but not cleanly according to the equation above. The products were mixtures, from which we could not isolate pure triphenyl-ω-haloalkylleads. In connection with this work, the corresponding α,ω-bis-(triphenyllead)-alkanes were prepared for comparison purposes. These compounds formed readily from excess triphenyllead–lithium and the polymethylene dihalide.

$$2(C_6H_5)_3PbLi + X(CH_2)_nY \longrightarrow (C_6H_5)_3Pb(CH_2)_nPb(C_6H_5)_3 + LiX + LiY$$

Tertiary Amino Groups.—Organolead compounds containing aminoaryl,[3b] alkylaminoaryl,[3a] dialkylaminoaryl[5] or trialkylamino[3a] groups have been described. These lead-containing amines are weak bases, and will dissolve in water only if the solution is rather strongly acid. Such strongly acid solutions are presumably undesirable for physiological work, besides which the C–Pb bond is quite sensitive to acid cleavage. A method was therefore sought for forming, from these lead-containing amines, hydrophilic structures which would bring them into solution in water at a *p*H close to 7.0. Since the quaternary ammonium hydroxides are strong bases, it appeared that their salts with strong acids should fulfill the require-

(1) E. I. du Pont Postgraduate Fellow, 1948–1950.

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