compound is readily soluble in benzene, slightly soluble in ethyl acetate, and very slightly soluble in ether and in petroleum ether.

Anal. Calcd. for $C_{29}H_{22}O_2$: C, 86.53; H, 5.51. Found: C, 86.27; H, 5.57. Subs., 0.5031: 11.93 cc. of 0.1 *N* NaOH. Calcd.: 12.50 cc.

α-Naphthyl-diphenyl-aminomethane.—Five g. of α-naphthyl-diphenyl-bromomethane was dissolved in benzene and the solution saturated with dry ammonia. The precipitated ammonium bromide was filtered off, the benzene evaporated, and the residue dissolved in ether from which the amine was obtained in large, colorless crystals; m. p., 168–169°; yield, 3.95 g., or 95%. The compound is readily soluble in benzene, slightly soluble in ether and very slightly soluble in alcohol and in petroleum ether.

Anal. Calcd. for $C_{23}H_{19}N$: N, 4.53. Found (Kjeldahl): 4.50.

Di-α-naphthyl-phenyl-aminomethane.[2]—Two and one-half g. of di-α-naphthyl-phenyl-bromomethane was dissolved in benzene and the solution saturated with dry ammonia. Following the above procedure, the amine was obtained from ether in small, colorless crystals; m. p., 164–165°; yield, 1.75 g., or 82%. The compound is readily soluble in benzene, somewhat soluble in ether and slightly soluble in petroleum ether and in alcohol.

Anal. Calcd. for $C_{27}H_{21}N$: N, 3.90. Found (Kjeldahl): 3.84, 3.89.

Summary

A convenient method for the preparation of triarylmethyl acetates has been described.

α-Napthyl-diphenyl-methyl acetate, di-α-napthyl-phenylmethyl acetate, and the corresponding triarylmethyl amines have been prepared and described.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMICAL RESEARCH, PARKE, DAVIS AND COMPANY, No. 31]

TETRA-ALKYL-SUCCINIMIDES AND THEIR PHARMACOLOGICAL ACTION

BY ARTHUR W. DOX

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On account of certain analogies in structure between the dialkyl-barbituric acids and other well-known hypnotics, on the one hand, and the tetra-alkyl-succinimides on the other hand, it was desired to prepare representatives of the latter for the purpose of determining their physiological action. It is commonly supposed that two alkyl groups, particularly ethyls, attached to the same carbon atom tend to impart hypnotic properties to the molecule. Numerous illustrations might be cited, including the simple ketones, the sulfonal series, the dialkyl derivatives of acetylurea I, hydantoin II and barbituric acid III, and the recently described dialkyl-

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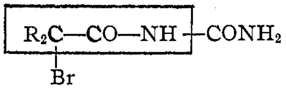
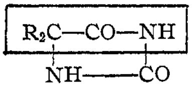
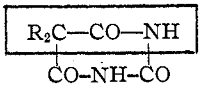
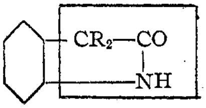
[2] The properties of this compound and also the method of preparation have been incorrectly described in a previous article, THIS JOURNAL, 44, 192 (1922).

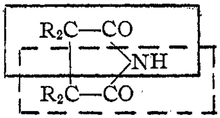
homophthalimides[1] IV. The grouping $R_2C<$ is thus very frequently met in synthetic hypnotics. Extending this grouping further, it will be seen that among the nitrogen-containing hypnotics the arrangement, $—CR_2—CO—NH—$, is strikingly prevalent. This latter grouping is present in a duplicated arrangement in the tetra-alkyl-succinimides V.


I
(Adalin)


II
(Nirvanol)


III
(Veronal)


IV


V

Molecular structure is, of course, not in itself a satisfactory basis for predicting physiological activity except in the case of closely related homologs. Practically all of the synthetic hypnotic drugs have certain physical properties conforming to the requirements of the Overton-Meyer theory of relative partition between the aqueous and the oil phase of an emulsion, and in all probability certain little understood phenomena of surface tension are likewise of importance in the manifestation of hypnotic activity. These, however, are properties which cannot definitely be determined in advance; hence, molecular structure is taken as the starting point when new drugs of possible therapeutic value are to be synthesized. In addition to certain similarities in structure, it was reasonable to assume that the tetra-alkyl-succinimides would further resemble the dialkyl-barbituric acids in their resistance to hydrolysis and oxidation, comparatively low melting points, greater solubility in organic solvents than in water, and in their ability to form soluble salts with alkali metals.

The tetramethyl derivative is the only tetra-alkyl-succinimide described in the literature. This was prepared by Auwers and Gardner[2] by heating the ammonium salt of the acid in a sealed tube. The ordinary method of preparing imides of dibasic acids by distillation of the ammonium salt gave in this case the anhydride instead of the imide. Of the various possible tetra-alkyl-succinic acids only four are known, the tetramethyl,[3] tetra-ethyl,[4] tetrapropyl,[5] and tetraphenyl.[6] The last is stated to be in-

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[1] Lumière and Perrin, *Compt. rend.*, **171**, 637 (1920).

[2] Auwers and Gardner, *Ber.*, **23**, 3623 (1890).

[3] Brown and Walker, *Ann.*, **274**, 48 (1893).

[4] Walker and Walker, *J. Chem. Soc.*, **87**, 965 (1905).

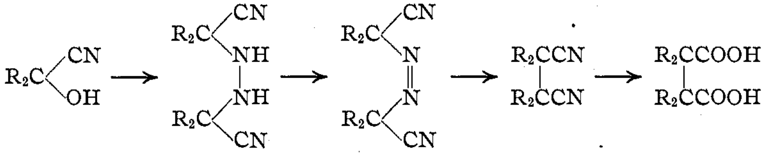
[5] Crichton, *J. Chem. Soc.*, **89**, 933 (1906).

[6] Klinger, *Chem.-Ztg.*, **34**, 1032 (1910).

capable of forming an anhydride; hence, its ability to form an imide is equally doubtful. On the other hand, the tetra-ethyl and tetrapropyl derivatives exhibit a most remarkable tendency to pass into anhydrides that are stable to strong alkali, a fact that argues for the stability of the corresponding imides.

Experimental Part

Direct alkylation of the esters of succinic acid is apparently not feasible because of the tendency to condense into esters of the cyclic succinosuccinic acid. Tetramethylsuccinic acid has been obtained in the form of its ethyl ester by the action of silver on ethyl α-bromo*iso*butyrate[7] by electrolysis of potassium monoethyl-dimethylmalonate[3] and as the free acid by decomposition and saponification of azo-dimethyl-acetonitrile.[8] The second method was applied successfully in the preparation of homologs, and the third method should also be capable of extension. Inasmuch as the present investigation had for its object the preparation of the imides for physiological test, no attempt was made to devise newer and more satisfactory methods of synthesis. The procedure employed by Thiele and Heuser for the preparation of the tetramethyl acid was applied to the preparation of the homologous dimethyl-diethyl- and tetra-ethyl-succinic acids which were then converted into the imides. It is based upon the condensation of the ketone cyanohydrin with hydrazine, oxidation of the resulting hydrazonitrile to the azonitrile and finally the expulsion of the azo nitrogen and saponification of the nitrile groups.



Azo-methylethyl-acetonitrile.—To a solution of 43.3 g. of hydrazine sulfate in 400 cc. of warm water, 32.7 g. of sodium cyanide in 100 cc. of water was added through a reflux condenser, and then gradually 42 g. of methylethyl ketone. Owing to liberation of heat during the reaction it was found advisable to cool the mixture by immersing the container in cold water. The flask was then tightly stoppered and shaken vigorously at frequent intervals during two days. A dark colored oil formed at the surface and finally became pale yellow. The oil was separated, the aqueous layer extracted twice with ether, and the combined oil and ether extract shaken twice with small portions of water. After removal of the ether by evaporation in a vacuum at a low temperature, about 55 g. of a pale yellow, viscous oil remained. This crude hydrazo-methylethyl-acetonitrile could not be obtained crystalline by cooling in a freezing mixture. Oxidation to the azo derivative was performed directly without further purification. The oily liquid was transferred to a 2-liter flask, diluted with 25 cc. of alcohol and acidified with 50 cc. of dil. hydrochloric acid. The mixture was then cooled in a bath of ice and stirred with a turbine during the addition of bromine water until a permanent yellow

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[7] Auwers and Meyer, *Ber.*, **22,** 2013 (1889).

[8] Thiele and Heuser, *Ann.*, **290,** 40 (1896).

color developed. Meanwhile, crystalline lumps formed and floated at the surface. These were filtered off and the filtrate, including some oily liquid enclosed by the lumps, was again treated with bromine. The total yield of crystals was 38.8 g. The product was purified by dissolving in alcohol during very slight warming and then cooling in a freezing mixture. After two crystallizations the product consisted of white prisms melting at 57°. It is soluble in alcohol and ether, but insoluble in water, and liberates hydrogen cyanide when the solutions are heated.

Anal. Subs., 0.1394: H_2O, 0.1019; CO_2, 0.3178. Subs., 0.1, 0.1: N_2, 27.7 cc., 27.6 cc. (736 mm., 28°). Calcd. for $C_{10}H_{16}N_4$: C, 62.50; H, 8.33; N, 29.17. Found: C, 62.18; H, 8.12; N, 29.42, 29.31.

Subs., 0.2, 0.2: 20.91, 20.71 cc. of 0.1 *N* acid. Found (Kjeldahl): N, 14.64, 14.49.

The Kjeldahl value represents therefore the CN nitrogen with complete loss of the azo nitrogen.

The mother liquor from the first crystallization contained a small amount of a heavy, pungent oil, probably the brominated ketone.

sym.-**Dimethyldiethyl-succinic Acid.**—This was obtained from the azo-methylethyl-acetonitrile by expulsion of the azo nitrogen and saponification of the nitrile groups in a single operation. Although a number of preparations were made, under slightly varying conditions, the yield was invariably low, owing to the simultaneous formation of a fatty acid. To 50 cc. of 75% sulfuric acid warmed in an oil-bath at 100°, 5 g. of the azo-nitrile was gradually added in small portions through an air condenser, and the evolution of gas allowed to subside after each addition. When the entire amount is added at once to the cold acid, no matter how carefully the temperature is raised, a violent reaction occurs causing a sudden puff of smoke through the condenser. After all of the azo-nitrile had been added the temperature of the bath was gradually raised to 125° and maintained at this point for two hours. The contents of the flask were then cooled, diluted with water and subjected to steam distillation. The distillate, consisting of dimethyldiethyl-succinic acid, its anhydride and a fatty acid by-product, was refluxed with an excess of sodium hydroxide and finally evaporated to dryness. The residue, when dissolved in water and acidified, gave white granular crystals that were freed from the fatty acid by washing with a little chloroform; yield, 1.5 to 2.0 g.; m. p., 147–148°, with evolution of gas (anhydride formation).

Anal. Subs., 0.1310: H_2O, 0.1070; CO_2, 0.2868. Calcd. for $C_{10}H_{18}O_4$: C, 59.40; H, 8.91. Found: C, 59.71; H, 9.08.

Dimethyldiethyl-succinic Anhydride

Heating the acid to its melting point converted it quantitatively into the anhydride. This distilled at 250–255° and remained liquid even after long standing. It has a strong camphoraceous odor.

Anal. Subs., 0.1923: H_2O, 0.1530; CO_2, 0.4624. Calcd. for $C_{10}H_{16}O_3$: C, 65.22; H, 8.70. Found: C, 65.58; H, 8.84.

The mother liquors from several preparations of dimethyldiethyl-succinic acid all contained an insoluble oil and had the odor characteristic of higher fatty acids. These were combined, extracted with ether, the solvent was evaporated and the residual oil distilled over a micro burner. The main portion boiled at 170–174°.

Anal. Subs., 0.1614: H_2O, 0.1402; CO_2, 0.3512. Calcd. for $C_5H_{10}O_2$: C, 58.82 H, 9.80. Found: C, 59.34; H, 9.65.

Analysis and boiling point identified the substance as *dl*-methylethyl-acetic acid. The amount recovered was approximately equal to that of the dimethyldiethyl-succinic acid.

***sym.*-Dimethyldiethyl-succinimide.**—Two g. of the acid was dissolved in an excess of concd. ammonium hydroxide and the solution evaporated in a vacuum at room temperature. The resulting crystals of the ammonium salt were then heated in a sealed tube at 170–175°. A sirupy liquid containing a few crystals remained in the tube. Extraction with ether, recrystallization from benzene and finally dilution of the alcoholic solution with water gave 1.35 g. of small, white crystals, possessing a camphoraceous odor; m. p., 93–94°. The substance is soluble in the ordinary organic solvents and in dilute alkali, but difficultly soluble in water.

Anal. Subs., 0.1712: N_2, 12.2 cc. (744 mm., 27°). Calcd. for $C_{10}H_{17}O_2N$: N, 7.65. Found: 7.66.

Azo-diethyl-acetonitrile.—The same procedure was followed as in the case of the lower homolog just described, using molecular proportions of diethyl ketone, hydrazine sulfate and sodium cyanide. The intermediate hydrazo derivative, as before, failed to crystallize, and the crude product (75.5 g. from 57.3 g. of ketone) was oxidized without further purification. The oxidation product consisted of 51.5 g. of white crystals which melted at 74–75° after two recrystallizations.

Anal. Subs., 0.1801: H_2O, 0.1457; CO_2, 0.4289. Subs., 0.1, 0.1: N_2, 24.6, 24.7 cc. (736 mm., 30°). Calcd. for $C_{12}H_{20}N_4$: C, 65.45; H, 9.09; N, 25.45. Found: C, 64.95; H, 8.99; N, 25.68, 25.79.

Subs., 0.2, 0.2: 18.07, 18.27 cc. of 0.1 *N* acid. Found (Kjeldahl): N, 12.65, 12.79.

As in the case of the lower homolog, the Kjeldahl determination accounts for only half of the nitrogen present.

Tetra-ethyl-succinic Acid.—This was prepared in essentially the same way as was the lower homolog. The decomposition temperature of the azo-nitrile was about 10° higher but, as before, the reaction was violent unless the material was added to the sulfuric acid in successive small portions. After the bath temperature had been maintained at 140° for some time the mixture was cooled and diluted. The crystals that separated were filtered, then treated with an excess of alkali, and an insoluble substance was filtered off. The filtrate when acidified gave 1.64 g. of small, white needles; m. p., 150–151°. The melting point reported by Walker and Walker was 149°.

Anal. Subs., 0.1497: H_2O, 0.1290; CO_2, 0.3446. Calcd. for $C_{12}H_{22}O_4$: C, 62.61; H, 9.57. Found: C, 63.03; H, 9.58.

Tetra-ethyl-succinonitrile.—The portion insoluble in alkali had a strong camphoraceous odor and was very volatile with steam. It was purified by steamd istillation and solidified in the condenser and receiver in large, flat prisms; m. p., 47°. Analysis showed it to be the unsaponified nitrile. The yield in this instance was 1.32 g.

Anal. Subs., 0.1171: H_2O, 0.1115; CO_2, 0.3221. Subs., 0.1278: N_2, 17.3 cc. (748 mm., 25°). Calcd. for $C_{12}H_{20}N_2$: C, 75.00; H, 10.42; N, 14.58. Found: C, 75.02; H, 10.58; N, 14.78.

The nitrile is quite resistant to hydrolysis, and when it is refluxed with acid or alkali considerable loss occurs through volatilization. Heating with hydrochloric acid in a sealed tube at 180°, however, converted it almost quantitatively into the acid anhydride.

The remarkable tendency of the acid to pass over to the anhydride, noted by Walker and Walker, was confirmed by the writer's experience. Mere recrystallization of the acid from hot chloroform gave a quantitative yield of the anhydride, which formed large, transparent crystals; m. p., 87°.

When the tetra-ethyl-succinic acid was prepared by steam distillation of the product of hydrolysis of the azo-nitrile, the distillate contained, in addition to the product sought, oily drops that failed to solidify and had the characteristic, rancid odor of fatty acids. Extraction of the oil with ether and distillation of the residue after evaporation of the solvent gave a liquid boiling at 190–193°. Boiling point and analysis identified the substance as diethylacetic acid.

Anal. Subs., 0.1470: H_2O, 0.1368; CO_2, 0.3370. Calcd. for $C_6H_{12}O_2$: C, 62.07; H, 10.34. Found: C, 62.52; H, 10.34.

Tetra-ethyl-succinimide.—An attempt to prepare this through the ammonium salt was unsuccessful. When the acid was dissolved in ammonium hydroxide and the solution carefully evaporated at a low temperature, a separation of anhydride began as soon as the excess of ammonia had disappeared. Evidently, the ammonium salt is hydrolyzed with ease and cannot be obtained in solid form from an aqueous solution. The imide was obtained, however, by heating 2 g. of the acid with 2 g. of ammonium carbonate in a sealed tube for seven hours at 175°. The product, which was mostly soluble in water, consisted of the ammonium salts of the acid and of the imide in about equal amounts. The separation was effected by precipitating with hydrochloric acid and dissolving in chloroform. The addition of petroleum ether then precipitated the acid in practically pure form. From the filtrate the chloroform was removed by spontaneous evaporation and the residue dissolved in alcohol. Addition of water then caused the imide to separate in white, scaly crystals; m. p., 104°. The substance has a camphor-like odor, particularly noticeable on warming it. It is soluble in the usual organic solvents and in dilute alkali, but nearly insoluble in water.

Anal. Subs., 0.1736: H_2O, 0.1558; CO_2, 0.4352. Subs., 0.1597: N_2, 9.5 cc. (748 mm., 27°). Calcd. for $C_{12}H_{21}O_2N$: C, 68.25; H, 9.95; N, 6.64. Found: C, 68.37; H, 9.97; N, 6.42.

Pharmacological Action

Both of the tetra-alkyl-succinimides described above, like the dialkylbarbituric acids, form soluble sodium salts which are easily administered intraperitoneally to white mice. With veronal (diethyl-barbituric acid) the effective dose is 0.3 mg. per g. of body weight. After a few minutes of preliminary excitement, a marked muscular incoördination develops, followed by complete narcosis lasting several hours. The same dose of tetra-ethyl-succinimide dissolved in the exact equivalent of sodium hydroxide and administered intraperitoneally caused marked excitement within two minutes, followed immediately by convulsions with arched back and rigid tail, and in twenty minutes the animal was dead. One-half this dosage (0.15 mg. per g.) produced violent convulsions recurring at frequent intervals during two hours, after which gradual recovery set in. At no time was there any evidence of narcotic or even sedative effect. The dimethyldiethyl derivative was somewhat less powerful but produced precisely the same symptoms. With the larger dose, death ensued about an hour later and with the smaller dose recovery began sooner. In a general way the action of these drugs is suggestive of strychnine poisoning. When tetra-ethyl-succinimide was administered orally to a dog in a dose of 0.1 g. per kilogram of body weight the effect was not observed until after about 45 minutes. A very marked muscular incoördination then set in which lasted about two hours. The pupils of the eye became dilated and it was evident that the animal's vision was impaired from the way the animal bumped into various objects in its path. Gradual recovery then set in and after a few hours the dog was apparently normal. There was no evidence of narcotic or sedative action. The effect was so different from that predicted on the basis of structural analogy that a possible specific effect of the imide grouping suggested itself, in spite of the fact that the dialkyl-homophthalimides are claimed to be hypnotics. Dr. Kamm[9] informed the writer that he had observed practically the same symptoms after administering the sodium salt of camphoric-imide intraperitoneally to mice.

Summary

Two tetra-alkyl-succinimides were prepared from the corresponding acids obtained by heating the azo-dialkyl-acetonitriles with sulfuric acid. When tested pharmacologically these two derivatives, in spite of certain structural analogies to a number of well-known hypnotics, were found to be quite toxic, the main symptoms being muscular incoördination and convulsions, without any evidence of sedative action.

Detroit, Michigan

NOTE

The Dissociation of Benzopinacol Derivatives.—In view of the fact that Löwenbein[1] has just published the statement that tetraphenyldicyanoethane dissociates, when heated, we would like to make a preliminary announcement regarding this substance.

Our work on the action of metallic sodium on aromatic aldehydes, ketones and esters[2] led us to anticipate that other groups, in addition to ONa and OC_6H_5,[3] when linked to a tetraphenylethylene group would produce compounds capable of dissociation into trivalent carbon radicals. In CN and $OCOC_6H_5$ it appears that we have found such groups. Tetraphenyldicyanoethane and the dibenzoyl derivative of benzopinacol develop an appreciable color when heated to about 150°. In molten naphthalene the color of the cyanide is an intense pink which disappears upon cooling and reappears when the solution is heated again; the dibenzoyl compound becomes yellow or orange when heated.

We are now engaged with the study of the anisyl and naphthyl analogs of these compounds; the latter we expected might dissociate at a lower temperature than the corresponding phenyl derivatives.

Contribution from the Chemical Laboratory
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[9] Dr. Oliver Kamm, private communication.

[1] Löwenbein, *Ber.*, **58**, 606 (1925).

[2] This Journal, **46**, 2560 (1924); **47**, 229 (1925).

[3] Schlenk and Weickel, *Ber.*, **44**, 1184 (1911). Schlenk and Thal, *Ber.*, **46**, 2841 (1913). Wieland, *Ber.*, **44**, 2550 (1911).