Anal. Calcd. for $C_{11}H_{13}N_3O_7S_1$: C, 39.88; H, 3.93; N, 12.68. Found: C, 40.20; H, 4.12; N, 12.37.

DNP-DL-Methionine Sulfone.—From 1.81 g. of DL-methionine sulfone and 1.85 g. of DNFB, 3.09 g. (89%) of the product was recrystallized from hot ethanol; m.p. 184.5° dec.

Anal. Calcd. for $C_{11}H_{13}N_3O_8S_1$: C, 38.04; H, 3.75; N, 12.10. Found: C, 38.15; H, 3.94; N, 11.97.

Bis-DNP-L-cysteine.—From 0.88 g. of L-cysteine·HCl·H_2O and 1.86 g. of FDNB, 2.29 g. (83%) of the product was obtained; it was recrystallized in CH_3COOH–H_2O and it melted with decomposition at 155–169°, $[\alpha]^{23}D$ −265.8° (1% $NaHCO_3$).

Anal. Calcd. for $C_{15}H_{11}N_5O_{10}S$: C, 39.74; H, 2.43; N, 15.45. Found: C, 39.97; H, 2.51; N, 15.50.

DNP-DL-Alanylglycylglycine.—By the same procedure, DNP peptides can be prepared in good yield. From 0.97 g. of DL-alanylglycylglycine (Nutritional Biochemical Corp., Cleveland, Ohio) and 0.89 g. of FDNB, 1.28 g. (72%) of the product was obtained after recrystallization in 50% aqueous ethanol; m.p. 205° dec.

Anal. Calcd. for $C_{13}H_{15}N_5O_8$: C, 42.28; H, 4.07; N, 18.97. Found: C, 41.37; H, 4.43; N, 18.53.

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1,2-Diphenyl-4-alkyl-3,6-diketohexahydropyridazines

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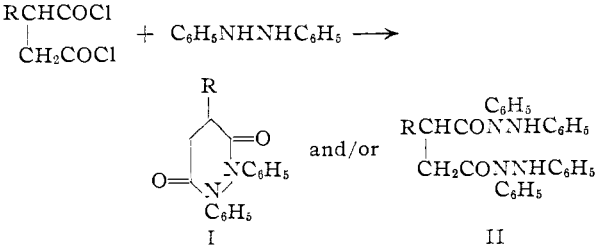
It has been reported that 1,2-diaryl-4-alkyl-3,5-diketopyrazolidines[1] possess analgesic, antipyretic, drug potentiating and anti-inflammatory activity,[1b,2] with an apparent peak of useful activity in 1,2-diphenyl-4-(*n*-butyl)-3,5-diketopyrazolidine, which is not without side-effects.[3] Because of some experience[4] with the six-membered ring structure, pyridazine, it seemed of interest to learn if the homologous 1,2-diphenyl-4-alkyl-3,6-diketohexahydropyridazines (I) possessed a pharmacological action similar to that of the corresponding diketopyrazolidines. A search of the literature revealed no compounds of this general structure. The description of the preparation of a few compounds of the desired type constitutes the subject of this paper.

Two obvious ways of preparing these compounds are (1) condensation of an α-alkylsuccinic ester with hydrazobenzene and (2) condensation of an α-alkylsuccinyl chloride with hydrazobenzene in the presence of a base. An attempt to cause a condensation of diethyl α-methylsuccinate with hydrazobenzene by heating them with sodium ethoxide at 150° resulted in a tarry mixture from which no crystalline material was obtained. When hydrazobenzene was added gradually to a mixture prepared by adding α-methylsuccinyl chloride to a solution of pyridine in ether, 1,2-diphenyl-4-methyl-3,6-diketohexahydropyridazine was formed in poor yield, although the crystalline product was easily isolated and purified. It then was found that when the order of mixing the reactants was reversed (*i.e.*, the α-methylsuccinyl chloride was added slowly to a solution of pyridine and hydrazobenzene in ether) the yield was increased to about 40%; consequently, this latter procedure was used to prepare the other compounds in the series. α-Ethylsuccinyl chloride also gave about a 40% yield of the corresponding 4-ethyl compound. α-(*n*-Propyl)-succinyl chloride gave a considerably lower yield (*ca.* 16%) and in addition there was isolated about an equal amount of a more soluble material whose analysis showed it to be the open-chain compound, α-(*n*-propyl)-N,N′,N″,N‴-tetraphenylsuccinic dihydrazide. When α-(*n*-butyl) succinyl chloride was allowed to react with hydrazobenzene under the same conditions the only crystalline product isolated was the open chain dihydrazide. We have not investigated whether this phenomenon of change in the amounts of isolated cyclic I and open chain II products, as the alkyl group increases from methyl to butyl, is caused by a change in the ease of crystallization of the products or whether the increase in bulk of the alkyl group actually hinders the ring formation.



α-(*n*-Propyl)-succinyl chloride and α-(*n*-butyl)-succinyl chloride are not reported previously in the literature; their preparation from the corresponding succinic acids and phosphorus pentachloride is described in the Experimental part of this paper.

Pharmacology.—The diketohexahydropyridazines and succinic dihydrazides herein described were administered orally to mice; in doses up to 2000 mg./kg. there were no deaths and no toxic signs. 1,2-Diphenyl-4-(*n*-propyl)-3,6-diketohexahydropyridazine and 1,2-diphenyl-4-ethyl-3,6-diketohexahydropyridazine did not demonstrate any analgesic activity in rats by the thermal radiation technique,[5] in oral doses of 500 and 200 mg./kg., respectively. They also did not show any antipyretic activity in rats, by the test procedure of Brownlee,[6] in oral doses of 400 mg./kg. We are indebted to Dr. John F. Reinhard and Miss Mary N. Lewis, of our Pharmacology Department, for these data.

The lack of pharmacological activity very probably indicates that the compounds are poorly absorbed; they are insoluble in water over a wide *p*H range. Since 1,2-diphenyl-4-(*n*-butyl)-3,5-diketo-

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pyrazolidine is absorbed rapidly[7] from the gastrointestinal tract one can assume that this is due to the enolizable methine group that is lacking in the six-membered homologs and in the succinic dihydrazides.

Experimental[8,9]

α-(*n*-Propyl)-succinyl Chloride.—α-(*n*-Propyl)-succinic acid[10] (57 g., 0.36 mole) was placed in a three-necked flask with a stirrer, reflux condenser and a wide rubber tubing connected to an erlenmeyer flask containing phosphorus pentachloride (150 g., 0.71 mole). The phosphorus pentachloride was added slowly to the stirred acid and when the addition was complete the reaction mixture was warmed until all the solid acid was dissolved. The mixture then was distilled under water-pump vacuum through a 10-inch helix-packed column giving α-(*n*-propyl)-succinyl chloride, boiling at 102–106° at 15 mm., yield 37 g. (53%).

Anal. Calcd. for $C_7H_{10}O_2Cl_2$: C, 42.66; H, 5.11. Found: C, 42.80; H, 5.29.

α-(*n*-Butyl)-succinyl Chloride.—By a procedure similar to the above α-(*n*-butyl)-succinic acid[11] was converted to α-(*n*-butyl)-succinyl chloride, boiling at 118° at 14 mm., yield 45%.

Anal. Calcd. for $C_8H_{12}O_2Cl_2$: C, 45.51; H, 5.73. Found: C, 45.39; H, 5.62.

1,2-Diphenyl-4-methyl-3,6-diketohexahydropyridazine.—In a three-necked flask fitted with a stirrer, reflux condenser and dropping funnel there was placed hydrazobenzene (9.2 g., 0.05 mole), pyridine (10 ml.) and dry benzene (150 ml.); in the dropping funnel there was placed α-methylsuccinyl chloride[12] (8.4 g., 0.05 mole) dissolved in dry benzene (50 ml.). The acid chloride was dripped into the hydrazobenzene solution over a half-hour period at room temperature and then the mixture was heated at reflux for one hour. The cooled reaction mixture was shaken with an excess of 1 *N* hydrochloric acid to remove pyridine and the organic layer was separated and stripped of solvent under vacuum. The solid residue was crystallized from ethanol, yielding a material melting at 183–184°, yield 6.0 g. (43%).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; N, 10.00. Found: C, 72.96; H, 5.91; N, 10.10.

1,2-Diphenyl-4-ethyl-3,6-diketohexahydropyridazine.—By a procedure similar to that used above, α-ethylsuccinyl chloride[13] was converted to 1,2-diphenyl-4-ethyl-3,6-diketohexahydropyridazine, in 40% yield, melting at 144–144.5°.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.60; H, 6.29; N, 9.56.

1,2-Diphenyl-4-(*n*-propyl)-3,6-diketohexahydropyridazine and α-(*n*-Propyl)-N,N′,N″,N‴-tetraphenylsuccinic Dihydrazide.—In a three-necked flask fitted with a stirrer, reflux condenser and a dropping funnel there was placed hydrazobenzene (25.3 g., 0.137 mole), pyridine (29 ml.) and dry ether (400 ml.) and in the dropping funnel there was placed α-(*n*-propyl)-succinyl chloride (27 g., 0.137 mole). The acid chloride was added slowly to the hydrazobenzene solution at room temperature and the resulting mixture was heated at reflux for two hours. The reaction mixture was cooled and shaken with excess of 1 *N* hydrochloric acid. The organic layer was evaporated to dryness and the solid residue was taken up in hot ethanol. On cooling, there were obtained crystals which weighed 6.5 g. (16%) and melted at 122.5–124.5°. A small sample, recrystallized from ethanol for analysis, melted at 126–127°.

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 74.18; H, 6.50; N, 9.10.

The mother liquor from the above crystals yielded a second crop of crystals weighing 7.5 g. (22%) and melting at 170–173°. A small sample was recrystallized from ethanol for analysis.

Anal. Calcd. for $C_{31}H_{32}N_4O_2$: C, 75.58; H, 6.55; N, 11.37. Found: C, 75.09; H, 6.52; N, 11.37.

α-(*n*-Butyl)-N,N′,N″,N‴-tetraphenylsuccinic Dihydrazide.—Following the same procedure used to prepare 1,2-diphenyl-4-methyl-3,6-diketohexahydropyridazine, α-(*n*-butyl)-succinyl chloride reacted with hydrazobenzene to give a 24% yield of material melting at 115–120°; this was recrystallized from ethanol to give a 16% yield of material melting at 122–124°; the material crystallized very slowly.

Anal. Calcd. for $C_{32}H_{34}N_4O_2$: C, 75.86; H, 6.76; N, 11.06. Found: C, 75.92; H, 6.83; N, 10.92.

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2,6-Di-*t*-butylbenzoquinone

BY S. J. METRO

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During an evaluation of the antioxidant properties of 2,6-di-*t*-butyl-*p*-cresol in lubricating oils, a yellow crystalline substance, m.p. 65–66°, which was identified as 2,6-di-*t*-butylquinone, was formed in the condenser of the test apparatus after a few days. This substance has been shown to result from the action of 2,2′-azoisobutyronitrile on 2,4,6-tri-*t*-butylphenol in the presence of oxygen.[1] The quinone forms a mono-2,4-dinitrophenylhydrazone and like the 2,5-isomer[2,3] forms a monoöxime. Its ultraviolet spectrum resembles that of benzoquinone, but its maximum (256 mμ) occurs at longer wave lengths. It shows strong absorption at 6.0 μ in the infrared.[4]

A number of other oxidation products of 2,6-di-*t*-butyl-*p*-cresol, such as 3,5-di-*t*-butyl-*p*-hydroxybenzaldehyde,[1] 1,2-bis-(3,5-di-*t*-butyl-4-hydroxylphenyl)-ethane and 3,5,3′,5′-tetra-*t*-butylstilbene,4,4′-quinone have been reported.[5–8]

Experimental

2,6-Di-*t*-butyl-1,4-benzoquinone (I).—The apparatus used for the oxidation consisted of a glass tube 600 mm. long and 45 mm. in diameter. The tube had a water condenser which extended 100 mm. down into the tube. Three hundred ml. of a 0.4–0.8% solution of 2,6-di-*t*-butyl-*p*-cresol in lubricating oil was placed in the tube along with 60 ml. of water and a coil of copper–iron catalyst. Oxygen was bubbled through the solution at a rate of 3.5 ± 0.5 liters per hour while the temperature was maintained at 95 ± 0.5°. After two or three days approximately 100 mg. of II formed on the condenser, m.p. 65–66°, λ_{max} 256, ε 15,400.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.10; O, 14.52; mol. wt., 220. Found: C, 76.61; H, 9.44; O, 14.43; mol. wt. (Rast), 219.

Monoöxime of 2,6-Di-*t*-butyl-1,4-benzoquinone.—Fifty mg. of 2,6-di-*t*-butyl-1,4-benzoquinone, 50 mg. of hydroxylamine hydrochloride, 3 ml. of pyridine and 5 ml. of absolute alcohol were refluxed for one hour on a steam-bath. The solvents were removed by evaporation in a current of nitro-

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(4) The infrared spectrum referred to in this paper has been deposited as Document number 4450 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting in advance $1.25 for photoprints, or $1.25 for 35 mm. microfilm payable to Chief, Photoduplication Service, Library of Congress.

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