TABLE I

3-ARYL-2-ARYLIMINO-4-THIAZOLIDONES AND THEIR SEMICARBAZONES

Imino-4-thiazolidones	Yield, %	M.p., °C.	Formula	Analyses: Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
3-α-Naphthyl-2-α-naphthyl-	82	172–173[a]	$C_{23}H_{16}N_2OS$	7.60	7.62	75.00	75.22	4.34	4.32
3-β-Naphthyl-2-β-naphthyl-	80	192–193[a]	$C_{23}H_{16}N_2OS$	7.60	7.56	75.00	75.26	4.34	4.33
3-*p*-Anisyl-2-*p*-anisyl-	82.5	107–108[b]	$C_{17}H_{16}N_2O_3S$	8.53	8.56	62.19	62.22	4.87	4.85
3-*p*-Phenetyl-2-*p*-phenetyl-	84	105–106[b]	$C_{19}H_{20}N_2O_3S$	7.86	7.84	64.04	64.12	5.61	5.60
Semicarbazones of imino-4-thiazolidones									
3-α-Naphthyl-2-α-naphthyl-	94	180[b]	$C_{24}H_{19}N_5OS$	16.47	16.45	67.76	67.80	4.47	4.46
3-β-Naphthyl-2-β-naphthyl-	90	200[b]	$C_{24}H_{19}N_5OS$	16.47	16.50	67.76	67.82	4.47	4.45
3-*p*-Anisyl-2-*p*-anisyl-	88	120[c]	$C_{18}N_{19}N_5O_3S$	18.18	18.26	56.10	56.30	4.93	4.94
3-*p*-Phenetyl-2-*p*-phenetyl-	84	110[d]	$C_{20}H_{23}N_5O_3S$	16.95	16.98	58.11	58.20	5.57	5.60

[a] After recrystallization from chloroform. [b] After recrystallization from absolute ethanol. [c] After recrystallization from benzene. [d] After recrystallization from ethanol.

Experimental

Preparation of Starting Materials.—The chemicals were obtained as follows: α-naphthylamine, β-naphthylamine, *p*-anisidine and *p*-phenetidine were obtained from Eastman Kodak Company, and monochloroacetic acid from Merck and Co., Inc. The compounds S-di-α-naphthylthiourea, S-di-β-naphthylthiourea, S-di-*p*-phenetylthiourea and S-di-*p*-anisylthiourea were prepared by the method of Rathke.[4] The homogeneity of each compound was established by conventional methods (b.p., m.p., etc.), before using it in the reaction. In all cases the physical constants of the disubstituted thioureas were in good agreement with the values given in the literature.

Preparation of 3-Aryl-2-arylimino-4-thiazolidones. General Procedure.—A mixture consisting of 0.02 mole of diaryl thiourea, 0.03 mole of monochloroacetic acid and 0.06 mole of anhydrous sodium acetate in 50 ml. of absolute ethanol was refluxed for two hours on the steam-bath. Toward the end of the condensation, some of the compound separated in leaflets. The crude reaction mixture was distilled to remove excess ethanol and poured into water to remove sodium chloride produced in the reaction and excess sodium acetate. The mixture was filtered, and the residue dried and crystallized from absolute ethanol. The melting point listed in the accompanying table remained unchanged on recrystallization from absolute ethanol or chloroform.

Preparation of Semicarbazones. General Procedure.—A mixture consisting of 0.001 mole of 3-aryl-2-arylimino-4-thiazolidone, 0.003 mole of semicarbazide hydrochloride and 0.006 mole of crystalline sodium acetate in 20 ml. of 95% ethanol was heated on the steam-bath for 15 minutes. The reaction mixture was poured into 50 ml. of water and filtered. The residue was washed with cold water, dried and crystallized from absolute ethanol or benzene for purposes of establishing melting point and analytical data, Table I.

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(4) Rathke, *Ber.*, **5**, 799 (1873).

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Derivatives of 2,4-Diphenylbutylamine and 2,4-Diphenylpyrrolidine

BY F. G. BORDWELL AND MARTIN KNELL[1]

In connection with another problem we wished to prepare 2,4-diphenylbutylamine. According to a report by Adkins and Whitman[2] this compound was obtained by the reduction of 4-nitro-1,3-diphenyl-1-butanone in dioxane solution with hydrogen and Raney nickel at 70–126° under a pressure of 150 atmospheres. Recently Kloetzel[3] reduced the same compound under similar conditions in methanol and described the product as 2,4-diphenylpyrrolidine. These investigators[2,3] apparently obtained similar products, since each reported the preparation of a phenylthiourea derivative melting at nearly the same point (191–191.5° *vs.* 189–190°).

Previous to these accounts Kohler and Drake[4] had obtained small quantities of the hydrochloride (m.p. 171–172°) and oxalate of 2,4-diphenylpyrrolidine by reduction of 4-nitro-1,3-diphenyl-1-butanone with hydrogen and a platinum catalyst. Identification was made on the basis of carbon and hydrogen analyses; there is usually a significant difference in the hydrogen content of derivatives of 2,4-diphenylpyrrolidine and 2,4-diphenylbutylamine, but not in the carbon or nitrogen content. Rupe and Gisiger[5] also isolated a small amount of the oxalate of 2,4-diphenylpyrrolidine from the reduction of 2,4-diphenyl-4-oxobutanenitrile with hydrogen and a large quantity of nickel catalyst. Carbon and hydrogen analyses were given for the oxalate and free base. From their base they prepared a hydrochloride (m.p. 154°) and a phenylthiourea (m.p. 188°) for which they gave nitrogen analyses.

Adkins and Whitman[2] made their structure assignment as a primary amine on the basis of the formation of a 3-nitrophthalimide[6] (in unstated yield). Kloetzel[3] claimed the absence of primary amines in the products from his reductions of γ-nitroketones in view of the failure of any portion of the benzenesulfonamides to dissolve in 10% aqueous sodium hydroxide. However, the benzenesulfonamides of many aryl–aliphatic primary amines are insoluble in aqueous alkali.[7] Neither Adkins and Whitman[2] nor Kloetzel[3] reported hydrogen analyses for their bases or derivatives. Kloetzel pointed out the similarity in melting point of the phenylthiourea (189–190°) to that given by Rupe and Gisiger[5] for the phenylthiourea of 2,4-diphenylpyrrolidine (188°), and the similarity in melting point of the

(1) National Institute of Health Predoctoral Fellow, 1947–1948.
(2) Adkins and Whitman, THIS JOURNAL, **64**, 150 (1942).
(3) Kloetzel, *ibid.*, **69**, 2271 (1947).
(4) Kohler and Drake, *ibid.*, **45**, 2144 (1923).
(5) Rupe and Gisiger, *Helv. Chim. Acta*, **8**, 349 (1925).
(6) Alexander and McElvain, THIS JOURNAL, **60**, 2285 (1938).
(7) Carothers, Bickford and Hurwitz, *ibid.*, **49**, 2908 (1927).

hydrochloride (168–170°) to that reported by Kohler and Drake[4] for the hydrochloride of 2,4-diphenylpyrrolidine (171–172°); but the melting point of the hydrochloride differed from that reported by Rupe and Gisiger (154°).[5] In order to establish the identity of the product from the reduction of 4-nitro-1,3-diphenyl-1-butane with hydrogen in the presence of a nickel catalyst, 2,4-diphenylbutylamine was prepared by an unambiguous route.

Experimental

Reduction of 10.2 g. (0.48 mole) of 2,4-diphenylbutanenitrile[8] in alcoholic hydrochloric acid solution using palladium chloride catalyst[9] gave 8.8 g. (69%) of **2,4-diphenylbutylammonium chloride**, m.p. 150–153°.[10] After crystallization from ethanol–ether and methanol–ether, the salt melted at 151.5–153°; this corresponds to the melting point of 154° reported by Rupe and Gisiger[5] for the hydrochloride of their reduction product, but not to that of Kohler and Drake[4] or to that of Kloetzel.[3]

Anal.[11] Calcd. for $C_{16}H_{19}NCl$: N, 5.35. Found: N, 5.52.

The **phenylthiourea** of 2,4-diphenylbutylamine was obtained as long, colorless needles after crystallization from absolute alcohol and alcohol–water; m.p. 117–117.5° (60% yield). This differs from the melting points reported by Adkins and Whitman,[2] Kloetzel,[3] and Rupe and Gisiger[5] for their phenylthioureas.

Anal. Calcd. for $C_{23}H_{24}N_2S$: C, 76.62; H, 6.71; N, 7.77. Found: C, 76.66; H, 6.68; N, 7.82.

The **3-nitrophthalimide** of 2,4-diphenylbutylamine, m.p. 125–126°, was obtained in 62% yield. Purification from benzene–petroleum ether gave yellow crystals, m.p. 127.5–128.5°. Adkins and Whitman[2] reported the preparation of a 3-nitrophthalimide (in unstated yield) melting at 129.5°.

Anal. Calcd. for $C_{24}H_{20}O_4N_2$: C, 71.99; H, 5.04; N, 7.00. Found: C, 71.60; H, 5.06; N, 6.86.

The **benzenesulfonamide** derivative of 2,4-diphenylbutylamine melted at 84–84.5° after crystallization from petroleum ether and from absolute alcohol. This derivative was not soluble in 10% aqueous sodium hydroxide. Kloetzel[3] obtained a benzenesulfonamide melting at 123–124°.

Anal. Calcd. for $C_{22}H_{23}O_2NS$: C, 72.24; H, 6.34. Found: C, 72.36; H, 6.53.

Repetition of the reduction of 4-nitro-1,3-diphenyl-1-butanone under conditions similar to those used by Adkins and Whitman[2] gave, after vacuum distillation, a crude amine which yielded 95% (based on 2,4-diphenylpyrrolidine) of a phenylthiourea derivative melting at 177–183°. Crystallization from absolute alcohol gave material melting at 189–190° (60% recovery), and a second crystallization from benzene–petroleum hexane raised the melting point to 190–191° (80% recovery). A benzenesulfonamide, m.p. 122–123°, agreeing with that reported by Kloetzel was also obtained. The reaction of the amine with 3-nitrophthalic anhydride gave some material insoluble in aqueous sodium bicarbonate. This material melted at 103–111°, but resisted attempts at further purification.

From these data it appears that the principal product obtained by hydrogenation of 4-nitro-1,3-diphenyl-1-butanone using Raney nickel catalyst is 2,4-diphenylpyrrolidine, as reported by Kloetzel.[3] However, the isolation of a 3-nitrophthalimide by Adkins and Whitman[2] corresponding in melting point to that of 2,4-diphenylbutylamine points to the presence of this material as a by-product, at least when dioxane is used as a solvent. Similarly, the isolation by Rupe and Gisiger[5] of a hydrochloride agreeing in melting point with that of 2,4-diphenylbutylamine indicates the formation of this compound along with 2,4-diphenylpyrrolidine in their reduction of 2,4-diphenyl-4-oxobutanenitrile. Evidently there is need for considerable caution in classifying aryl–aliphatic amines as primary or secondary on the basis of derivatives.

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(8) Newman, THIS JOURNAL, **62**, 870 (1940).

(9) Perez-Medina, Mariella and McElvain, *ibid.*, **69**, 2574 (1947).

(10) Melting points are uncorrected.

(11) Analyses were by Margaret Hines and Virginia Hobbs.

A New Synthesis of Dimethyl-β-propiothetin Hydrochloride[1]

BY N. F. BLAU AND C. G. STUCKWISCH[2]

Recent reports[3–5] concerning the methyl-donating capacity of certain sulfonium compounds in given biological systems indicate the probable importance of dimethylthetin and dimethyl-β-propiothetin in the normal animal economy and suggest, furthermore, the possible therapeutic utility of these substances in the treatment of some types of metabolic abnormalities. Out of such considerations there arose in this Laboratory a need for the ready synthesis of considerable quantities of dimethyl-β-propiothetin. The work of Gresham and associates[6] has demonstrated the ability of the alcoholic carbon of β-propiolactone to react with various nucleophilic reagents and thus to lead to a large number of β-substituted derivatives of propionic acid. It seemed likely that under suitable conditions dimethyl sulfide would attack the β-carbon of β-propiolactone to yield dimethyl-β-propiothetin. Such has proved to be the case.

Experimental

Nitromethane (100 ml.) was placed in a 250-ml. graduated cylinder provided with gas inlet and exit tubes, 15.5 g. (0.25 mole) of dimethyl sulfide was introduced and 18 g. (0.25 mole) of β-propiolactone (supplied by B. F. Goodrich Chemical Company) was added slowly with constant stirring. There was no perceptible rise in temperature. The cylinder was tightly stoppered and the mixture allowed to stand overnight. A slow stream of dry hydrogen chloride was then passed through the cylinder, previously cooled in an ice-bath to about 10–15°, until a solid mass of the hydrochloride of dimethyl-β-propiothetin was precipitated (about 15–20 minutes). During the passage of the hydrogen chloride the temperature was allowed to rise about 10° over the initial level, but never above 40°, in order to minimize the rate of polymerization of the lactone. This desideratum could further be promoted by the employment of a larger volume of the solvent, nitromethane.[7] The gain in weight of the cylinder at this juncture was usually found to be close to 90% of an equivalent of hydrogen chloride absorbed. The crystalline product was separated by filtration (with suction) and washed well on the filter with cold acetone. The crude crystalline product was dissolved

(1) Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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(3) V. du Vigneaud, A. W. Moyer and J. P. Chandler, *J. Biol. Chem.*, **174**, 477 (1948).

(4) J. W. Dubnoff and H. Borsook, *ibid.*, **176**, 797 (1948).

(5) F. A. Maw and V. du Vigneaud, *ibid.*, **176**, 1037 (1948).

(6) T. L. Gresham, J. E. Jansen and F. W. Shaver, THIS JOURNAL, **72**, 72 (1950).

(7) Since the completion of our synthesis, the projected outline of which we had communicated to T. L. Gresham, he kindly advised us of his use of acetonitrile as a solvent in this procedure.