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.

in hot ethanol, acetone was added to incipient turbidity and the product was allowed to crystallize in the refrigerator. A yield of 75–78% was usually obtained. The crystals melted with decomposition at 129° (Fisher–Jones melting point apparatus). A mixed melting point with an authentic specimen[8] showed no depression. Potentiometric measurements gave theoretical values for neutralization equivalent and the compound analyzed correctly for sulfur and chlorine.

A further crop of impure product could be obtained by continued treatment of the clear mother liquor with dry hydrogen chloride (3–4 g.) and precipitation with acetone. By-products which invariably form are now being investigated.

(8) M. F. Ferger and V. du Vigneaud, *J. Biol. Chem.*, **185**, 53 (1950).

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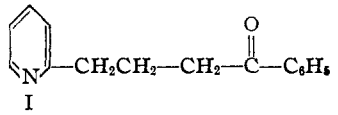
Muscular Relaxant Drugs. Some Substituted Pyridyl Ketones[1,2]

BY V. BOEKELHEIDE AND J. H. MASON

In a previous publication[3] it was reported that phenyl γ-(2-pyridyl)-propyl ketone (I) and the corresponding carbinol were effective as central depressants in causing muscular relaxation. Because of the pharmacological interest in compounds having such action, we have prepared some related compounds in an attempt to determine the structural requirements necessary for activity in this series.



I

Those compounds, which have not previously been reported, are given in Table I. The ketones were prepared by the Michael condensation of 2- or 4-vinylpyridine with the appropriate active methylene compound following the general method reported earlier.[4] The tertiary carbinol (VIII) was obtained *via* the Grignard reaction whereas the secondary carbinols resulted from reduction of the corresponding ketones.

Although none of the compounds prepared in this study were as potent as I, compounds II, III and VIII possessed appreciable muscular relaxant activity, indicating the non-specific nature of this type of drug action. Details of the pharmacology will be reported elsewhere.[5]

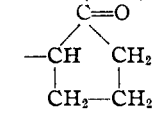
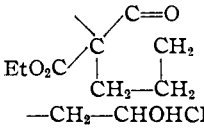
Experimental[6]

Michael Condensations.—These condensations were carried out according to the procedure previously described for the preparation of diethyl ethyl-β-(2-pyridyl)-ethylmalonate.[4] The additions of phenylacetone, 2-carbethoxycyclopentanone and desoxybenzoin to 2-vinylpyridine were carried out on a 0.3 molar scale and gave the desired adducts in yields of 32, 42 and 46%, respectively.

Compound VI, the adduct of 2-vinylpyridine and 2-carbethoxycyclopentanone, was converted to the simple ketone, V, by boiling 17.3 g. of the material under reflux with 87 ml. of 20% hydrochloric acid for four hours. After the reaction mixture had been made basic, it was extracted with ether and the ethereal extract was dried and then concentrated. Distillation of the residue gave 8.5 g. (68%) of V.

TABLE I

COMPOUNDS OF THE TYPE $PyCH_2CH_2R_1$

Cpd.	Py	R_1	M.p. or b.p.	Mm.	$n^{21}D$	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
II	4-Pyridyl	$-CH_2CO-C_6H_5$	77–79			$C_{15}H_{15}NO$	79.97	80.01	6.71	6.69
III	2-Pyridyl	$-CH(C_6H_5)-CO-CH_3$	130	0.1	1.5550	$C_{16}H_{17}NO$	80.30	79.82	7.16	7.19
IV	2-Pyridyl	$-CH(C_6H_5)-CO-C_6H_5$	74–75			$C_{21}H_{19}NO$	83.69	83.94	6.35	6.48
V	2-Pyridyl		114	0.1	1.5231	$C_{12}H_{15}NO$	76.15	75.68	7.99	8.33
VI	2-Pyridyl		120	0.1	1.5089	$C_{15}H_{19}NO_3$	68.94	68.46	7.33	7.55
VII	2-Pyridyl	$-CH_2-CHOHCH_3$	83	0.1	1.5128	$C_{10}H_{15}NO$	72.67	72.39	9.15	9.38
VIII	2-Pyridyl	$-CH_2-C(OH)(CH_3)-C_6H_5$	74–75			$C_{10}H_{19}NO$	79.63	79.86	7.94	8.18
IX	2-Piperidyl	$-CH_2CH(OH)-C_6H_5$	151	0.3	1.5434	$C_{15}H_{23}NO$	77.20	77.45	9.94	9.69

DERIVATIVES OF THE COMPOUNDS IN TABLE I

Cpd.	Type of derivative	Recrystn. solvent	M.p., °C.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
II	Picrate	Alcohol	140–141	$C_{21}H_{18}N_4O_8$	55.51	55.33	3.99	4.23
III	Picrate	Alcohol	131–132	$C_{22}H_{20}N_4O_8$	56.41	56.45	4.30	4.15
IV	Picrate	Alcohol	164–166	$C_{27}H_{22}N_4O_8$	61.13	61.24	4.15	4.26
V	Styphnate	Alcohol	140–141	$C_{10}H_{18}N_4O_9$	49.77	49.72	4.18	4.28
VI	Picrolonate	Alcohol	152–154	$C_{25}H_{27}N_5O_8$	57.14	57.08	5.18	5.25
VIII	Picrate	Alcohol	120–121	$C_{22}H_{22}N_4O_8$	56.16	56.02	4.71	5.06

In the preparation of II, the addition of ethyl benzoylacetate to 4-vinylpyridine, following the same general procedure, gave a dark red oil which decomposed on attempted distillation. The crude oil was, therefore, subjected to acid hydrolysis without further purification using the same hydrolysis procedure as in the preparation of V. In this case concentration of the ethereal extract gave a white solid.

(1) Aided by a grant from the National Foundation for Infantile Paralysis.

(2) Abstracted from the B.S. thesis of J. H. M.

(3) V. Boekelheide and E. J. Agnello, THIS JOURNAL, **72**, 5005 (1950).

(4) V. Boekelheide and S. Rothchild, *ibid.*, **71**, 879 (1949).

(5) We are indebted to Dr. I. H. Slater of the School of Medicine and Dentistry, University of Rochester, Rochester, New York, for the pharmacological testing.

(6) Analyses by Miss C. King and the Micro-Tech Laboratories.