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).

RESEARCH LABORATORY
VETERANS ADMINISTRATION CENTER
WICHITA, KANSAS

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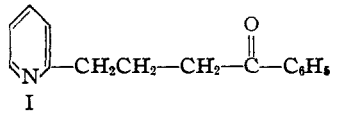
Muscular Relaxant Drugs. Some Substituted Pyridyl Ketones[1,2]

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]

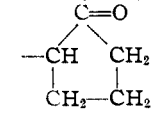
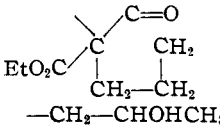
Experimental[6]

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	$C_{10}H_{13}N_4O_9$	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.

Recrystallization of the solid from ethanol gave II as white crystals, m.p. 77–79°, in 51% over-all yield.

2-Phenyl-5-(2′-pyridyl)-pentanol-2 (VIII).—To 100 ml. of a 2.0 *M* ethereal solution of phenylmagnesium bromide there was added dropwise with stirring a solution of 14.4 g. of 1-(2′-pyridyl)-4-pentanone[4] in 100 ml. of dry ether. The mixture was boiled under reflux for one hour and was then decomposed by addition of an aqueous ammonium chloride solution. The ether layer was removed, dried and concentrated. The resulting residual oil crystallized after standing for a month. Recrystallization of this solid from pentane gave 11.0 g. (50%) of II as white crystals, m.p. 70–72°. The same product was obtained when the addition of methylmagnesium iodide to phenyl γ-(2-pyridyl)-propyl ketone[3] was carried out in a similar manner.

5-(2′-Pyridyl)-pentanol-2, VII.—To 25 ml. of a 0.8 *M* ethereal solution of lithium aluminum hydride there was added dropwise with stirring a solution of 7.0 g. of 1-(2′-pyridyl)-pentanone-4 in 50 ml. of dry ether. After the solution had been boiled under reflux for fifteen minutes, moist ether was added and the precipitate of metallic hydroxides was removed. The ethereal solution was dried, concentrated and the residual oil was distilled yielding 5.0 g. (71%) of a colorless oil.

1-Phenyl-4-(2′-piperidyl)-butanol-1, IX.—A solution of 8.0 g. of 1-phenyl-4-(2′-pyridyl)-butanol-1,[3] 0.1 g. of platinum oxide, 30 ml. of ethanol and 60 ml. of 1.7 *N* hydrochloric acid was subjected to hydrogenation at room temperature and 3 atm. pressure of hydrogen. The absorption of three molar equivalents of hydrogen was complete in three and one-half hours. The catalyst and part of the solvent were then removed, the aqueous solution was made basic, and the oil which separated was taken up in benzene. After removal of the benzene, the residue was distilled to yield 5.2 g. (63%) of a colorless viscous oil.

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UNIVERSITY OF ROCHESTER
ROCHESTER, NEW YORK RECEIVED DECEMBER 4, 1950

The Synthesis of 2-Sulfanilamido-5-aminopyrimidine

BY WILLIAM T. CALDWELL

Although there are many substituted sulfanilamides and, indeed, many substituted sulfanilamidopyrimidines, there has been no record of the preparation of 2-sulfanilamido-5-aminopyrimidine. One reason for this is the fact that various devices for obtaining the compound by conventional or direct procedures all fail. From these may be singled out for mention the vain attempts to convert 2-amino-5-nitropyrimidine into a sulfonamide by the action of either *p*-nitrobenzenesulfonyl chloride or acetylsulfonyl chloride in pyridine, quinoline or other solvents, in the hot or cold, in spite of the fact that 2-acetamido-5-nitropyrimidine was easily obtained by warming with acetic anhydride. Other instances of a similar refractory behavior have been observed.[1] This paper describes the somewhat circuitous path by which the desired product was synthesized.

The author is grateful to Eli Lilly and Company for carrying out pharmacological tests, reports on which will appear elsewhere.

Experimental

2-Acetamido-5-benzamidopyrimidine.—The brownish solid residue obtained (after removing the solvent under diminished pressure without access of air) by catalytic reduction with platinum oxide instead of palladium on charcoal[2] of 30.7 g. of 2-acetamido-5-nitropyrimidine was treated in the cold with an excess (30 cc.) of benzoyl chloride followed by 310 cc. of 1.2 *N* aqueous potassium hydroxide, making sure that the mixture had an alkaline reaction. The buff or khaki-colored precipitate stood overnight in this alkaline medium and then was filtered off in a sintered glass funnel and washed well with cold water. A small sample was recrystallized from alcohol, using Darco, and yielded colorless to very pale yellow needles, that melted at 281–284° (uncor.) to a brown liquid; yield of crude product, 39.2 g. or 90%.

Anal.[3] Calcd. for $C_{13}H_{12}N_4O_2$: N, 21.85. Found: N, 21.31.

2-Amino-5-benzamidopyrimidine.—The residue of 2-acetamido-5-benzamidopyrimidine (39 g.) was boiled for exactly 30 minutes with 170 cc. of 1.1 *N* aqueous potassium hydroxide. During this boiling, the character of the crystals changed in appearance; after cooling thoroughly, filtering through sintered glass and washing well with ice-water, 22 g. (air-dried) of olive colored crystals were obtained. This material was boiled with 900 cc. of water (with Darco); upon filtering and cooling, lustrous white crystals of 2-amino-5-benzamidopyrimidine (IV) separated; m.p. 214–217° (uncor.).

Anal. Calcd. for $C_{11}H_{10}N_4O$: N, 26.12. Found: N, 26.13.

2-Acetylsulfanilamido-5-benzamidopyrimidine.—A solution of 17 g. of acetylsulfanilyl chloride in 35 cc. of dry pyridine was added slowly to a solution of 15.3 g. of 2-amino-5-benzamidopyrimidine in 50 cc. of dry pyridine in an ice-bath. After standing overnight at 45–50° there was a deposit of chunky crystals beneath a reddish-brown liquid. This cake of crystals was broken up with a stirring rod, shaken well and, after another four hours at 50°, had set to a thick porridge of crystals. The material was then heated for one hour on a steam-bath whereupon it became lighter in color, turning a canary yellow. After filtering off the solid and washing well with cold water, the creamy white product melted, after drying overnight at 110°, at 286–293° (uncor.); yield 68.2%. In several other runs, procedures and conditions were varied but yields remained at 68–69%.

Anal. Calcd. for $C_{19}H_{17}N_5O_4S$: N, 17.01. Found: N, 16.85.

2-Sulfanilamido-5-aminopyrimidine.—Although hydrolysis of 2-acetylsulfanilamido-5-benzamidopyrimidine to the final product proceeded satisfactorily with small amounts (5–10 g.) when refluxed overnight with twice the theoretical amount of 1.1 *N* 50% aqueous methanolic potassium hydroxide, it proved desirable to reflux a larger amount (38.9 g.) somewhat longer with 2.2 *N* 50% aqueous methanolic potassium hydroxide. After neutralizing with acetic acid, the product upon recrystallizing from water in which it is, surprisingly enough, even less soluble than "sulfadiazine" in the cold, was obtained as white needles; m.p. 256–259° (uncor.); yields 70–80%.

Anal. Calcd. for $C_{10}H_{11}N_5O_2S$: C, 45.28; H, 4.18; N, 26.40. Found: C, 45.19; H, 4.05; N, 26.58.

(1) English, Clark, Shepherd, Marson, Krapcho and Roblin, THIS JOURNAL, **68**, 1041 (1946).

(2) Roblin, Winnek and English, *ibid.*, **64**, 569 (1942).

(3) All analyses by Clark Microanalytical Laboratory, Urbana, Illinois.

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Rhodanine Derivatives[1]

BY FRANCES C. BROWN, CHARLES K. BRADSHER, SARA M. BOND AND MARNY POTTER

The compounds listed in Table I were prepared by the condensation of rhodanine or 3-substituted rhodanines with the appropriate aldehyde or ketone. The reactions, except as noted, were effected in an ethanol–ammonium hydroxide mix-

(1) The compounds were prepared under a contract with the Medical Division, Chemical Corps, U. S. Army.