[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES AND THE CHEMICAL LABORATORIES OF TEMPLE UNIVERSITY]

Claisen-like Condensation Reactions with 2,4,6-Trimethylpyrimidine

BY HUGH R. SULLIVAN AND WILLIAM T. CALDWELL

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2,4,6-Trimethylpyrimidine was condensed with ethyl benzoate and phenyl acetate by a Claisen-type condensation to 2,6-dimethyl-4-phenacylpyrimidine and 4-acetonyl-2,6-dimethylpyrimidine. An alternate procedure, the reaction of 2,6-dimethyl-4-pyrimidylmethyllithium with benzonitrile, yielded the 2,6-dimethyl-4-phenacylpyrimidine. It was proven that the 4-methyl group of 2,4,6-trimethylpyrimidine also is reactive in aldol condensations rather than the 2-methyl as postulated previously.[1] 4-Phenacyl- and 4-acetonyl-2,6-dimethylpyrimidine were converted to the corresponding oximes and then by catalytic reduction to the 4-(β-aminophenylethyl)-2,6-dimethyl- and 4-(β-aminopropyl)-2,6-dimethylpyrimidines. The condensation of 2,4,6-trimethylpyrimidine with ethyl oxalate yielded two compounds tentatively identified as 2,6-dimethyl-4-ethoxalylpyrimidine and 1,4-bis-(2,6-dimethyl-4-pyrimidyl)-2,3-butanedione.

The possibility of 2,4,6-trimethylpyrimidine undergoing a Claisen-like condensation reaction was indicated by the theoretical considerations of Roberts[2] on the reactivity of methyl groups of heterocyclic tertiary bases. This possibility also was substantiated by the fact that a number of investigators have performed Claisen-like condensation reactions on certain nitrogen heterocyclic compounds that are analogous to 2,4,6-trimethylpyrimidine. The investigations of Weiss and Hauser[3] on the acetylation, aroylation and carbethoxylation of α-picoline, quinaldine and lepidine using sodamide or potassium amide are examples.

2,4,6-Trimethylpyrimidine was first synthesized independently in 1937, by Bowman[4] and by Kondo and Yanai[5] from the condensation of acetylacetone and acetamidine hydrochloride. Relatively few investigations on condensation reactions involving 2,4,6-trimethylpyrimidine have been published. A number of workers have studied the condensation of 2,4,6-trimethylpyrimidine with benzaldehyde.

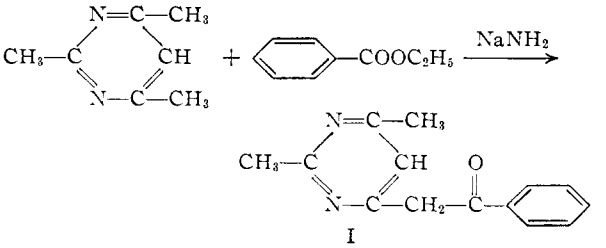
The condensation of 2,4,6-trimethylpyrimidine with benzaldehyde using zinc chloride as a catalyst was reported by Bowman[4] and by Kondo and Yanai.[5] The latter had ozonized the condensation product, 2,4,6-tristyrylpyrimidine, to the 2,4,6-pyrimidine trialdehyde which subsequently was oxidized to yield 2,4,6-pyrimidinetricarboxylic acid.

In a later work by Ochaia and Yanai,[1] 2,4,6-trimethylpyrimidine was condensed with one mole of benzaldehyde using zinc chloride to obtain a monocondensation product which was thought to be 2-styryl-4,6-dimethylpyrimidine. The proof of the structure was based upon the ozonization of this pyrimidine compound to the corresponding aldehyde with subsequent oxidation to the dimethylpyrimidinecarboxylic acid. This acid did not depress the melting point of 4,6-dimethylpyrimidine-2-carboxylic acid prepared using the procedure of Gabriel and Colman.[6] This work indicates that the most reactive methyl group of 2,4,6-trimethylpyrimidine is the one attached in the 2-position.

During the course of investigating the reaction of phenyllithium on various pyrimidines, Heyes and Roberts[7] found that phenyllithium reacted with 2,4,6-trimethylpyrimidine to yield 2,6-dimethyl-4-pyrimidylmethyllithium. The structure of the lithium compound was established by first allowing it to react with *n*-dodecyl bromide to give 2,6-dimethyl-4-(*n*-tridecyl)-pyrimidine in fair yields. This pyrimidine compound was reduced and then hydrolyzed to yield acetaldehyde which was isolated and identified as the 2,4-dinitrophenylhydrazone. The isolation of acetaldehyde, instead of *n*-tetradecylaldehyde, indicated that initially the phenyllithium had attacked the methyl group attached to the 4-position and not the 2-position of the pyrimidine ring.

Since there was a possibility of attack of the phenyllithium on the unsubstituted 5-position of the pyrimidine ring, Roberts[8] further synthesized 2,6-dimethyl-4-ethylpyrimidine in a similar manner, treating 2,6-dimethyl-4-pyrimidylmethyllithium with methyl bromide. An independent synthesis of this compound then established its structure

In the present work 2,4,6-trimethylpyrimidine, prepared using the procedure of Bowman,[4] was condensed with ethyl benzoate using sodamide in refluxing benzene.



I

The product 2,6-dimethyl-4-phenacylpyrimidine (I), after purification by acid–base extraction and distillation, was a red oil. 4-Acetonyl-2,6-dimethylpyrimidine also was prepared in a similar manner using phenyl acetate in an ether–benzene solution.

The assignment of the structure of these two condensation products as the 4-substituted-2,6-dimethylpyrimidines was indicated by the synthesis of 2,6-dimethyl-4-phenacylpyrimidine by an independent route. This other route was the reaction of 2,6-dimethyl-4-pyrimidylmethyllithium, prepared using Roberts' technique, with benzonitrile. The hydrolyzed product, 2,6-dimethyl-4-phenacylpyrimidine, when converted to its hydrochloride salt not only had the identical melting point but did not depress the melting point of the hydrochloride of the compound I prepared using the sodamide

(1) E. Ochiai and M. Yanai, *J. Pharm. Soc. Japan*, **58**, 76 (1938).
(2) J. C. Roberts, *Chem. and Ind.*, **66**, 658 (1947).
(3) M. Weiss and C. Hauser, THIS JOURNAL, **71**, 2025 (1949).
(4) A. Bowman, *J. Chem. Soc.*, 494 (1937).
(5) H. Kondo and M. Yanai, *J. Pharm. Soc. Japan*, **57**, 173 (1937).
(6) S. Gabriel and J. Colman, *Ber.*, **32**, 1531 (1899).
(7) T. D. Heyes and J. C. Roberts, *J. Chem. Soc.*, 328 (1951).
(8) J. C. Roberts, *ibid.*, 3065 (1952).

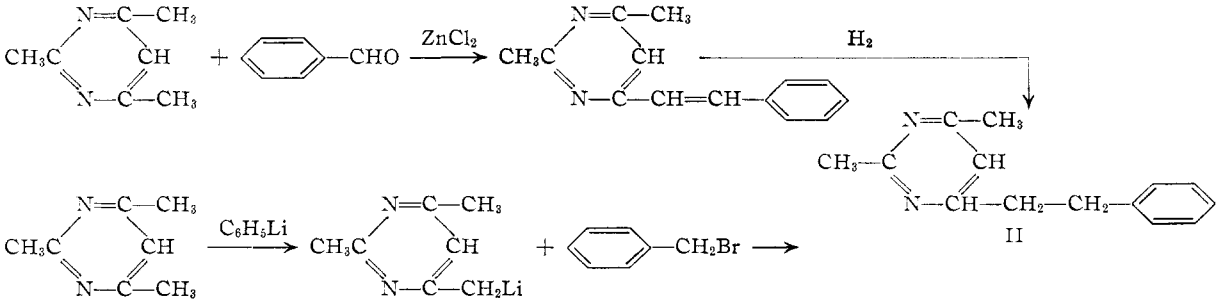
condensation of 2,4,6-trimethylpyrimidine and ethyl benzoate.

In an attempt to relate the work of Yanai, *et al.*,[1,5] to that of Roberts,[2,8] it was decided that the 4,6-dimethyl-2-(β-phenylethyl)-pyrimidine and 2,6-dimethyl-4-(β-phenylethyl)-pyrimidine should be synthesized.

The proposed 4,6-dimethyl-2-(β-phenylethyl)-pyrimidine was prepared by the catalytic reduction of the 4,6-dimethyl-2-styrylpyrimidine which was synthesized, using the procedure of Ochiai and Yanai,[1] by the condensation of benzaldehyde with 2,4,6-trimethylpyrimidine.

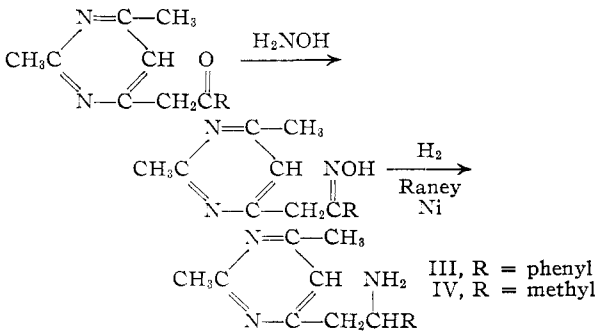
The 2,6-dimethyl-4-(β-phenylethyl)-pyrimidine was synthesized by the reaction of 2,6-dimethyl-4-pyrimidylmethyllithium, prepared using Roberts' technique, with benzyl bromide.

A comparison of the hydrochlorides of the 2,6-dimethyl-4-(β-phenylethyl)-pyrimidine and the previously presumed 4,6-dimethyl-2-(β-phenylethyl)-pyrimidine revealed that these compounds have identical melting points, infrared spectra and X-ray diffraction patterns. A mixed melting point did not depress the melting point of either compound.

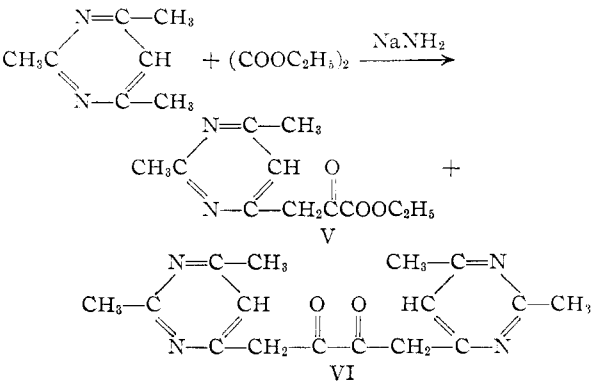


The preparation of 2,6-dimethyl-4-(β-phenylethyl)-pyrimidine (II) using both Roberts' pyrimidylmethyllithium and Yanai's dimethylstyrylpyrimidine indicates that the most reactive methyl group in 2,4,6-trimethylpyrimidine is indeed the one in the 4-position of the pyrimidine ring.

The investigation was now directed to the preparation of pyrimidine compounds analogous to benzedrine.



The 4-acetonyl- and 4-phenacyl-2,6-dimethylpyrimidine were converted to the corresponding oximes by treating them with hydroxylamine hydrochloride in a pyridine–ethanol solution similarly to the procedure of Bachmann and Boatner.[9] These oximes, isolated as hydrochloride salts, then were reduced catalytically using Raney nickel catalyst to obtain 4-(β-aminophenylethyl)-2,6-dimethylpyrimidine (III) and 4-(β-aminopropyl)-2,6-dimethylpyrimidine (IV). These compounds, isolated as their maleate salts, are being tested for possible pharmacological action.



The condensation of ethyl oxalate with 2,4,6-trimethylpyrimidine using sodamide also was accomplished successfully. The reaction yielded not only the desired 2,6-dimethyl-4-ethoxalylmethylpyrimidine (V) but also a material of high molecular weight having an empirical formula $C_{16}H_{18}N_4O_2$. The structure of 1,4-bis-(2,6-dimethylpyrimidyl)-2,3-butandione (VI) has been assigned to it as a result of infrared and ultraviolet data obtained.

Two unsuccessful attempts were made to prepare 4-acetonyl-2,6-dimethylpyrimidine by the condensation of ketene with 2,4,6-trimethylpyrimidine.

Acknowledgment.—The authors are indebted to Messrs. W. L. Brown, H. L. Hunter and G. M. Maciak for the microanalyses.

Experimental[10]

2,4,6-Trimethylpyrimidine.—This compound was prepared using the procedure of Bowman.[4] A solution of 175 g. (1.85 moles) of acetamidine hydrochloride, 229.0 g. (2.28 moles) of acetylacetone and 490.0 g. of potassium carbonate in 1.2 l. of water was allowed to stand at room temperature for two weeks. The solution then was saturated with 510 g. of potassium carbonate and the phases separated. The saturated aqueous phase was extracted with two 300-ml. portions of ether. The organic phase combined with the ether extracts was dried over anhydrous potassium carbonate for 24 hours. After filtering, the solvent was removed by distillation at atmospheric pressure and the residue distilled *in vacuo*. The product, 2,4,6-trimethylpyrimidine, boiled at 58–60° (11.0 mm.), 73.3 g. (32.4%).

2,6-Dimethyl-4-phenacylpyrimidine, Method A.—This compound was prepared by a method similar to that used by Weiss and Hauser[3] with α-picoline. In a 300-ml. three-

(9) W. E. Bachmann and C. N. Boatner, THIS JOURNAL, **58**, 2097 (1936).

(10) Melting points and boiling points are uncorrected.

necked flask, fitted with a Dry Ice condenser and a stirrer, were placed 100 ml. of liquid ammonia and a small crystal of ferric nitrate which acts as a catalyst for the formation of sodamide. To this solution 2.3 g. (0.10 g. atom) of metallic sodium was added with stirring. After complete reaction, indicated by the disappearance of the blue color, a solution of 6.1 g. (0.05 mole) of 2,4,6-trimethylpyrimidine in 50 ml. of sodium dried benzene was added dropwise during 30 minutes. After adding a further 100 ml. of dry benzene dropwise and replacing the Dry Ice condenser with a cold water condenser fitted with a drying tube, the reaction mixture was allowed to stand overnight at room temperature to evaporate the ammonia. After warming to 50° for three hours to remove the residual ammonia, 12.0 g. (0.08 mole) of ethyl benzoate was added dropwise with stirring to the reaction mixture. The color of the reaction mixture changed from green to yellow during the addition of the ethyl benzoate. After refluxing for 18 hours, the reaction mixture was decomposed by the careful addition of 50 ml. of water. The organic phase was separated and then extracted with four 50-ml. portions of 6 *N* hydrochloric acid. The combined aqueous acid extract was washed with ether and then saturated with sodium bicarbonate to yield a yellow oil. This oil was taken up in ether and dried over anhydrous magnesium sulfate. The ether was removed *in vacuo* to yield 6.1 g. of a residual yellow oil. This oil was distilled *in vacuo* to yield 2.0 g. of 2,4,6-trimethylpyrimidine which boiled at 43–44° (2.0 mm.). The desired 2,6-dimethyl-4-phenacylpyrimidine boiled at 146–150° (0.7 mm.), $n^{25}D$ 1.6512, 2.5 g. (22%).

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.28. Found: C, 74.21; H, 6.82; N, 11.67.

A solution of 0.6 g. of the base in ether was treated with anhydrous hydrogen chloride. The hydrochloride, 0.58 g., recrystallized twice from a methanol–ethyl acetate solution, melted at 223–224° dec.

Anal. Calcd. for $C_{14}H_{14}N_2O \cdot HCl$: C, 63.99; H, 5.75; N, 10.66; Cl, 13.50. Found: C, 63.87; H, 5.86; N, 10.48; Cl, 13.86.

Method B.—2,6-Dimethyl-4-phenacylpyrimidine also was prepared using 2,6-dimethyl-4-pyrimidylmethyllithium and benzonitrile. In a 500-ml. three-necked flask, fitted with a reflux condenser, stirrer, and swept with nitrogen, was placed 200 ml. of sodium-dried ether. Lithium squares, 0.85 g. (0.12 g. atom), were cut from clean lithium ribbon directly into the ether and then 9.4 g. (0.06 mole) of bromobenzene was added dropwise over a period of 30 minutes. After complete reaction, a solution of 6.1 g. (0.05 mole) of 2,4,6-trimethylpyrimidine in 50 ml. of dry ether was added dropwise. The reaction mixture became very red in color and deposited a dark red gummy material on the sides of the flask. After complete addition the reaction mixture was refluxed for 15 minutes during which time more gummy material precipitated from solution. After cooling, 5.2 g. (0.05 mole) of benzonitrile was added and the resulting solution refluxed for 1.5 hours. During this time the gummy red material slowly dissolved to give a light red solution. The reaction mixture was allowed to stand overnight and then decomposed by careful addition of 50 ml. of water. The ether phase was then extracted with two 100-ml. portions of 1 *N* hydrochloric acid. The combined acid aqueous solution, after washing once with ether, was made alkaline with concentrated ammonium hydroxide to yield a dark red oil. This oil was taken up in ether, dried over anhydrous magnesium sulfate, filtered, and the ether removed *in vacuo*. The residual oil distilled *in vacuo* gave the desired 2,6-dimethyl-4-phenacylpyrimidine which boiled at 170–171° (0.40 mm.), 5.0 g. (43%). The base was then converted to the hydrochloride salt with anhydrous hydrogen chloride and after three recrystallizations from methanol–ethyl acetate the hydrochloride melted at 223–224° dec.

Anal. Calcd. for $C_{14}H_{14}N_2O \cdot HCl$: C, 63.99; H, 5.75; N, 10.66; Cl, 13.50. Found: C, 64.13; H, 6.11; N, 10.63; Cl, 13.73.

4-Acetonyl-2,6-dimethylpyrimidine.—This compound was prepared using a procedure identical to that of method A for the preparation of 2,6-dimethyl-4-phenacylpyrimidine. 2,4,6-Trimethylpyrimidine, 97.6 g. (0.80 mole), was allowed to react with 18.4 g. (0.80 g. atom) of sodium in dry ether and benzene solution. Phenyl acetate, 54.0 g. (0.40 mole), then was added to the reaction mixture and the product was isolated and distilled, b.p. 75–76° (0.50 mm.), 20.0 g. (31%).

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.82; H, 7.37; N, 17.06. Found: C, 65.65; H, 7.31; N, 16.99.

The hydrochloride salt was prepared and recrystallized from acetone–ether.

Anal. Calcd. for $C_9H_{12}N_2O \cdot HCl$: N, 13.96; Cl, 17.67. Found: N, 13.72; Cl, 17.88.

2,6-Dimethyl-4-ethoxalylmethylpyrimidine.—The procedure was the same as that described in method A for 2,6-dimethyl-4-phenacylpyrimidine. Calcium chloride dried ethyl oxalate, 43.8 g. (0.30 mole), was allowed to react with a solution of sodamide prepared from 4.6 g. (0.20 g. atom) of sodium and 23.1 g. (0.20 mole) of 2,4,6-trimethylpyrimidine in ether. The reaction mixture was decomposed by careful addition of 400 ml. of 6 *N* hydrochloric acid. After washing with ether, the aqueous phase was neutralized with 1 *N* ammonium hydroxide and the red oil taken up in ether using a continuous liquid–liquid extractor. After drying over anhydrous magnesium sulfate, the ether solution was filtered and the ether then removed by distillation. The residue was crystallized from an ether–Skellysolve A solution to yield 1.0 g. of yellow crystalline product, which was tentatively identified as 1,4-bis-(2,6-dimethyl-4-pyrimidyl)-2,3-butanedione from analytical and spectral data and after two recrystallizations from benzene, melted at 231–232° dec., 0.9 g. (3.0%).

Anal. Calcd. for $C_{16}H_{18}N_4O_2$: C, 64.43; H, 6.08; N, 18.78. Found: C, 64.80; H, 6.02; N, 18.76.

The filtrate, from which the above product was crystallized, was concentrated *in vacuo* to dryness to yield the desired 2,6-dimethyl-4-ethoxalylmethylpyrimidine which, after two recrystallizations from ethyl acetate–Skellysolve A, melted at 108–109°, 5.0 g. (12.0%).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.52; H, 6.40; N, 12.79. Found: C, 59.45; H, 6.30; N, 12.61.

2,6-Dimethyl-4-(β-phenylethyl)-pyrimidine.—In a manner identical with that used in method B for 2,6-dimethyl-4-phenacylpyrimidine, 25.7 g. (0.15 mole) of benzyl bromide was added to an ether solution of 2,6-dimethyl-4-pyrimidylmethyllithium prepared from 18.3 g. (0.15 mole) of 2,4,6-trimethylpyrimidine and 2.6 g. (0.36 g. atom) of lithium squares in 300 ml. of ether. The reaction yielded a red oil which on distillation gave the desired 2,6-dimethyl-4-(β-phenylethyl)-pyrimidine, b.p. 120° (0.50 mm.), $n^{25}D$ 1.5500, 11.9 g. (37.4%).

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.20; H, 7.60; N, 13.20. Found: C, 78.93; H, 7.49; N, 13.16.

The hydrochloride salt was prepared using anhydrous hydrogen chloride and after three recrystallizations from methanol–ethyl acetate melted at 185–186°.

Anal. Calcd. for $C_{14}H_{16}N_2 \cdot HCl$: C, 67.60; H, 6.89; N, 11.26; Cl, 14.25. Found: C, 67.75; H, 6.96; N, 10.93; Cl, 14.05.

Dimethylstyrylpyrimidine.—Essentially the procedure of Ochaia and Yanai[1] was followed to prepare this compound. In a sealed tube, a mixture of 12.2 g. (0.100 mole) of 2,4,6-trimethylpyrimidine, 9.9 g. (0.093 mole) of benzaldehyde and 2.0 g. of zinc chloride was heated at 100° for four hours. After cooling, the reaction mixture was dissolved in a hot benzene–ethanol solution and then taken to dryness *in vacuo*. The residue was redissolved in hot benzene and then ether added until solution became turbid. Upon chilling, 5.0 g. of product crystallized and was collected. After two recrystallizations from benzene–ether solutions the product melted at 177–178°, 4.3 g. (14.5%), and is the distyrylmethylpyrimidine reported by Ochaia and Yanai[1] to be the by-product of the reaction.

The ether–benzene filtrate from the isolation of the distyrylpyrimidine was taken to dryness *in vacuo* and the residue dissolved in dilute hydrochloric acid. The aqueous solution, after washing with ether, was made alkaline with concentrated ammonium hydroxide and the resulting oil extracted in ether and dried over magnesium sulfate. The ether solution was then treated with anhydrous hydrogen chloride and the hydrochloride of the dimethylstyrylpyrimidine, after four recrystallizations, melted at 194–195°, 6.0 g. (30%). A solution of 1.0 g. of this hydrochloride in 10 ml. of water was made alkaline with concentrated ammonium hydroxide, the oil extracted in ether and dried over magnesium sulfate. The ether was removed *in vacuo* and the residue, dimethylstyrylpyrimidine, after two recrystalli-

zations from Skellysolve A, melted at 57–58°, 0.70 g. (70%). The melting point reported by Ochiai and Yanai[1] was 57–58°.

Reduction of Dimethylstyrylpyrimidine.—A solution of 3.0 g. (0.012 mole) of the dimethylstyrylpyrimidine hydrochloride and 200 ml. of ethanol was catalytically reduced with 47 lb./sq. in. of hydrogen using a 5% palladium-on-carbon catalyst. The solution was then filtered and the solvent removed *in vacuo*. The dimethyl-β-(phenylethyl)-pyrimidine hydrochloride, after three recrystallizations from methanol–ethyl acetate solutions, melted at 185–186°, 1.9 g. (63%). A mixed melting point with the 2,6-dimethyl-4-(β-phenylethyl)-pyrimidine hydrochloride prepared from 2,6-dimethyl-4-pyrimidylmethyllithium and benzyl bromide melted at 185–186°—no depression of melting point.

4-Acetonyl-2,6-dimethylpyrimidine Oxime.—This compound was prepared using a procedure similar to that of Bachmann and Boatner.[9] In a 300-ml. flask fitted with a reflux condenser were placed 12.1 g. (0.074 mole) of 4-acetonyl-2,6-dimethylpyrimidine, 12.1 g. (0.174 mole) of hydroxylamine hydrochloride, 50 ml. of dry pyridine and 50 ml. of absolute ethanol. This mixture was refluxed for three hours, then the solvents removed *in vacuo* and the residue dissolved in a solution of nine parts of acetone and one part of ethanol. This solution was then treated with anhydrous hydrogen chloride which precipitated the insoluble 4-acetonyl-2,6-dimethylpyrimidine oxime dihydrochloride. The product, after three recrystallizations from methanol–ethyl acetate solutions, melted at 172–173°, 9.0 g. (47%).

Anal. Calcd. for $C_9H_{13}N_3O\cdot 2HCl$: C, 42.87; H, 5.96; N, 16.67; Cl, 28.12. Found: C, 42.75; H, 5.70; N, 16.27; Cl, 27.69.

2,6-Dimethyl-4-phenacylpyrimidine Oxime.—This compound was prepared using the same procedure of Bachmann and Boatner.[9] The mixture of 22.5 g. (0.32 mole) of 2,6-dimethyl-4-phenacylpyrimidine, 22.5 g. (0.68 mole) of hydroxylamine hydrochloride, 110 ml. of dry pyridine and 110 ml. of absolute ethanol gave the desired 2,6-dimethyl-4-phenacylpyrimidine oxime which was isolated as the hydrochloride salt. Its melting point, after recrystallization from methanol–ethyl acetate, was 222–223°, 15.0 g. (54%).

Anal. Calcd. for $C_{14}H_{15}N_3O\cdot HCl$: C, 60.54; H, 5.81; N, 15.12; Cl, 12.75. Found: C, 60.81; H, 5.97; N, 15.03; Cl, 12.46.

4-(β-Aminopropyl)-2,6-dimethylpyrimidine.—A mixture of 5.7 g. (0.042 mole) of 4-acetonyl-2,6-dimethylpyrimidine oxime dihydrochloride, 200 ml. of absolute ethanol and 2.0 g. of Raney nickel was reduced under 50 lb. of hydrogen for 36 hours. The solution was filtered and the solvent removed *in vacuo* to give a solid residue. This residue was dissolved in water, washed with ether and then made alkaline with 50% sodium hydroxide to yield a light yellow oil which was taken up in ether, dried over anhydrous magnesium sulfate and then treated with maleic acid to form the maleate salt. The 4-(β-aminopropyl)-2,6-dimethylpyrimidine maleate, recrystallized from methanol–ethyl acetate, melted at 130–131°, 2.0 g. (18%).

Anal. Calcd. for $C_{13}H_{19}N_3O_4$: C, 55.50; H, 6.81; N, 14.94. Found: C, 55.45; H, 7.13; N, 14.83.

4-(β-Aminophenylethyl)-2,6-dimethylpyrimidine.—Using the identical procedure that was used to prepare the 4-(β-aminopropyl) derivative, 3.15 g. (0.0114 mole) of 2,6-dimethyl-4-phenacylpyrimidine oxime hydrochloride was reduced to yield the desired 4-(β-aminophenylethyl)-2,6-dimethylpyrimidine which was isolated as the maleate salt also. After two recrystallizations from methanol–ethyl acetate, the product melted at 170–171° dec., 1.0 g. (25%).

Anal. Calcd. for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.17; N, 12.24. Found: C, 63.14; H, 5.79; N, 12.20.

PHILADELPHIA, PENNSYLVANIA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Antispasmodics. VI. Pyrrolidylalkyl Esters and their Quaternary Salts[1]

BY ROBERT BRUCE MOFFETT, JOHN L. WHITE, BROOKE D. ASPERGREN AND FRANK E. VISSCHER

RECEIVED OCTOBER 27, 1954

Twenty-five new hydrochlorides and fourteen new quaternary salts of pyrrolidyl and substituted pyrrolidylalkyl esters were prepared. Their antispasmodic activities are reported, and some of the quaternary salts are among the most active known. A number also were tested for gastric antisecretory activity and four were found to be exceptionally active.

The high antispasmodic activity of some of the esters of methyl substituted pyrrolidylethanol, reported in paper V[2] of this series, prompted us to expand this series. Thus a number of new esters of 2-(2,2-dimethyl-1-pyrrolidyl)-ethanol, and one ester of 2-(2,2-dimethyl-1-pyrrolidyl)-propanol were prepared. In addition a series of pyrrolidylethyl esters substituted with three methyl groups, with an ethyl group, and with both methyl and ethyl groups were made.

The hydrochlorides of these basic esters were tested for antispasmodic activity (Table I). In all cases they were less potent than some of the compounds previously reported.[2]

In recent years a number of quaternary salts of anticholinergic compounds have been successfully introduced for the treatment of peptic ulcer and other ailments of the gastro-intestinal tract. It has long been known that quaternization of this type of compound generally increases its antispasmodic activity but this is usually offset by increase in toxicity. We have prepared quaternary salts of a number of the pyrrolidylalkyl esters herein or previously reported. In most cases no increase in antispasmodic therapeutic ratio was noted. However, with the most active compounds (*e.g.*, methyl bromide salts of nos. 17 and 18, Table I) a considerable increase in therapeutic ratio was observed.

Since the secretion of acid gastric juice is believed to have a deleterious effect on peptic ulcers it is desirable to test anticholinergic compounds for their antisecretory activity. Some of the compounds included in this study were so tested, and four of them (the quaternary salts of nos. 1, 4, 17 and 18, Table I) had an exceptionally high order of activity. In general it seems that the quaternary salts give a much more favorable antisecretory therapeutic ratio than the hydrochlorides.

The free basic esters (Table II) and their hydrochlorides (Table III) were prepared by methods

(1) Reported in part before the Division of Medicinal Chemistry, A.C.S. at Los Angeles, California, March, 1953, Abstracts, p. 8L.

(2) R. B. Moffett and J. H. Hunter, THIS JOURNAL, **74**, 1710 (1952).