hydrochloric acid, and the insoluble hydrochloride treated according to the directions given above. An additional 1.68 g. of 1-phenacyl-2-benzylthio-4-phenylimidazole, m. p. 136–139°, was obtained. The total yield of crude product was 7.01 g. or 73%. One crystallization from dilute alcohol gave 6.37 g. of material, m. p. 141.5–142.5°. A mixture with the previously prepared sample showed no depression of melting point. This same product can be made in 78% yield by alkylating 2-benzylthio-4(5)-phenylimidazole with phenacyl bromide in alcohol in the presence of sodium bicarbonate.

The picrate of 1-phenacyl-2-benzylthio-4-phenylimidazole was prepared by mixing the base and picric acid in hot alcohol, m. p. 169–171°.

Anal. Calcd. for $C_{30}H_{23}N_5O_9S$: C, 58.72; H, 3.78. Found: C, 58.90; H, 3.74.

2-Thiol-4(5)-phenylimidazole.—Red phosphorus (3.7 g.) was added to 15 g. of iodine in 25 ml. of glacial acetic acid, and the resulting suspension was heated under reflux for twenty minutes. Then 3.00 g. of 2-benzylthio-4(5)-phenylimidazole was added and the solution was heated under reflux for three and one-half hours. The solution was filtered to free it from phosphorus, decolorized with sodium bisulfite, diluted with two volumes of water, and neutralized with ammonium hydroxide. The resulting suspension was cooled in ice, and the product was separated from the solution by filtration. To free the 2-thiol-4(5)-phenylimidazole from starting material, it was dissolved in 50 ml. of 10% sodium hydroxide solution. After separating the insoluble 2-benzylthio-4(5)-phenylimidazole (0.34 g., m. p. 172–175°), the filtrate was neutralized with 8 ml. of glacial acetic acid, and cooled. On filtration 1.13 g. (64% on the basis of the starting material consumed) of 2-thiol-4(5)-phenylimidazole, m. p. 249–255°, was obtained. Crystallization of the compound from a mixture of acetone and benzene raised its melting point to 261–262°. The picrate, formed in absolute alcohol, crystallized as garnet-red prisms, m. p. 178–179° (dec.). For further identification of 2-thiol-4(5)-phenylimidazole was oxidized with dilute nitric acid to 4(5)-phenylimidazole, m. p. 130–131°; 4(5)-phenylimidazole nitrate, m. p. 167–167.5° (dec.). These physical constants agree well with those previously recorded for these compounds.[8,13]

Summary

1. It has been shown that the reaction of S-benzylisothiourea with phenacyl bromide can form any one of four products, 2-amino-4-phenylthiazole, benzyl phenacyl sulfide, 2-benzylthio-4-(5)-phenylimidazole and 1-phenacyl-2-benzylthio-4-phenylimidazole, depending upon the conditions of the reaction.

2. The 2-benzylthio-4(5)-phenylimidazole was cleaved to the known 2-thiol-4(5)-phenylimidazole by the action of acetyl iodide.

(13) R. L. Grant and F. L. Pyman, *J. Chem. Soc.*, **119**, 1893 (1921).

MINNEAPOLIS 14, MINNESOTA RECEIVED APRIL 16, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Synthesis of Some Substituted 2-Thiouracils

BY HENRY GILMAN AND H. SMITH BROADBENT

Considerable interest has developed within the last few years in the treatment of hyperthyroid disturbances by chemical means.[1] Among the most effective substances employed have been 2-thiouracil and some of its derivatives. In the course of a study of the chemotherapeutic properties of several types of nitrogen and sulfur containing compounds, it was decided, therefore, to synthesize several derivatives of 2-thiouracil for examination.

The 6-substituted-2-thiouracils were prepared by the usual method of condensing β-oxo esters with thiourea in the presence of sodium ethoxide.

Three different methods were employed in the preparation of the necessary β-oxo esters. They were the alkylation of ethyl acetoacetate, the Claisen condensation of esters, and the carbethoxylation of ketones with ethyl carbonate.

By alkylating sodio ethyl acetoacetate with γ-diethylaminopropyl chloride and with γ-diethylaminopropyl β-chloroethyl sulfide, the respective β-oxo esters, 1-diethylamino-4-carbethoxyhexanone-5 and 1-(γ-diethylaminopropylmercapto)-3-carbethoxypentanone-4, were prepared, isolated, and some of their important physical constants determined as well as those of some of their precursor compounds.

We were unable to condense successfully these two complex β-oxo esters with thiourea to form 2-thiouracils by the usual procedures. Only polymeric, gummy residues, quite unlike the probable properties of the expected compounds, were obtained. Anderson, *et al.*,[2] report the formation of unidentified by-products in considerable amount in preparing some of the longer chain (butyl, *n*-amyl, *n*-hexyl) 6-substituted-2-thiouracils. The yields in these condensations are not high at best.

The α-,β-, and γ-pyridoylacetates were prepared by the Claisen condensation of the pyridinecarboxylic acid esters and ethyl acetate. Although these β-oxo esters have been reported heretofore,[3,4,5,6] it was found possible to prepare the first two of them in greatly improved yields by a suitable modification of the Claisen condensation procedure using benzene as a diluent. The preparation of the necessary sodium ethoxide *in situ* in benzene suspension also obviates the necessity of preparing fresh, anhydrous, solid sodium ethoxide for the condensation as is usually done. The isolation of pure liquid ethyl picolinoylacetate does not appear to have been done. Pinner[3] isolated it as its sodium salt; Burrus and Powell[4] obtained it as

(1) Roblin, *Chem. Rev.*, **38**, 255 (1946).

(2) Anderson, Halverstadt, Miller and Roblin, THIS JOURNAL, **67**, 2197 (1945).

(3) Pinner, *Ber.*, **34**, 4237 (1901).

(4) Burrus and Powell, THIS JOURNAL, **67**, 1468 (1945).

(5) Bloom, Breslow and Hauser, *ibid.*, **67**, 2207 (1945).

(6) Miller, Dessert and Anderson, *ibid.*, **70**, 500 (1948).

TABLE I

2-THIOURACIL DERIVATIVES

Compound	Procedure	M. p., °C.[a]	Yield, %	Recrystallized from	Formula	Analyses, % N Calcd.	N Fd.	S Calcd.	S Fd.
6-(α-Pyridyl)-2-thiouracil	A	291–294 dec.	29	Gl. AcOH	$C_9H_7ON_3S$	20.48	20.70		
6-(β-Pyridyl)-2-thiouracil[b]	A	296–298 dec.	38	Gl. AcOH	$C_9H_7ON_3S$	20.48	20.42		
6-(γ-Pyridyl)-2-thiouracil	A	355–358 dec.	50	[d]	$C_9H_7ON_3S$			15.62	15.73
6-(p-Methoxylphenyl)-2-thiouracil[c]	A	285–288 dec.	31	Gl. AcOH	$C_{11}H_{10}O_2N_2S$	11.96	12.10		
6-(α-Thienyl)-2-thiouracil	A	293–296 dec.	30.5	Gl. AcOH	$C_8H_6ON_2S_2$	13.3	13.6		
2-(γ-Diethylaminopropyl-mercapto)-4-hydroxy-6-methylpyrimidine	B	B. p. 183–188° (0.4 mm.)	82	.....	$C_{12}H_{21}ON_3S$	16.46	16.65		
2-(p-Nitrobenzylmercapto)-4-hydroxy-6-methyl-pyrimidine	B	220–221	89	Dioxane–water	$C_{12}H_{11}O_3N_3S$			11.56	11.32
2-(p-Nitrophenethylmercapto)-4-hydroxy-6-methylpyrimidine	B	Softens 222 Melts 224–226 dec.	62	Dioxane–propanol	$C_{13}H_{13}O_3N_3S$			11.01	11.08

[a] All melting points were taken on a Berl–Kullman block. [b] Two years after this work was completed the preparation of this compound was reported by others.[6,8] The first group gives its melting point as 296–298°. The second gives *ca.* 291°. [c] Two years after this work was completed, the preparation of this compound was reported by others[8] who report its melting point as 226–227°, a value we were unable to substantiate. [d] Insoluble in all ordinary organic solvents. It was purified by dissolving it in alkali, filtering, reprecipitating with acetic acid, and washing with water.

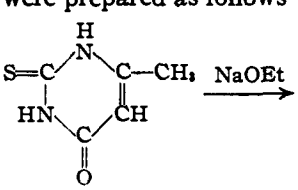
its hydrochloride; however, it was found possible to distil the free base with little decomposition and isolate the slightly impure liquid, which can be kept for a long time with very little change.

The method of Camps[7] has usually been used in esterifying the pyridinecarboxylic acids. He reports yields of 90, 90 and 91%, respectively, for the α-, β- and γ-isomers; however, later workers have not been able to duplicate his yields. Burrus and Powell[4] obtained yields of 61 and 30% of the β- and γ-isomers, respectively, by Camps' method. We were able to prepare ethyl nicotinate in 72% yield by Camps' method. By employing a different esterification procedure, ethyl isonicotinate was conveniently secured in 61.4% yield.

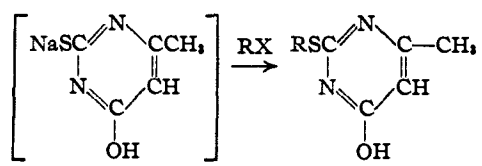
The 6-pyridyl-2-thiouracils (see table) are very high melting solids, quite insoluble in organic solvents. In fact, the γ-isomer is almost completely insoluble in acetic acid, nitrobenzene, carbitol, aniline, pyridine, quinaldine, tri-*n*-butyl phosphate, and all common solvents at their boiling temperatures; however, all three of them are readily soluble in strong acids and bases.

Ethyl *p*-anisoylacetate and ethyl β-(2-thienyl)-oxopropionate were prepared by the carbethoxylation with ethyl carbonate and sodamide of the corresponding ketones. The former tends to decompose on distilling even at low pressures.

Mercapto derivatives of 6-methyl-2-thiouracil were prepared as follows



(7) Camps, *Arch. Pharm.*, **240**, 346 (1902).



Neither *o*- nor *p*-nitrobromobenzene were found to be sufficiently reactive to undergo metathesis in our hands with a suspension of the sodium salt of the thiouracil in absolute ethanol, although they will readily condense with ordinary sodium mercaptides under such conditions. With 2,4-dinitrochlorobenzene a very insoluble product was secured; however, its isolation in a pure form was not accomplished.

γ-Diethylaminopropyl chloride, *p*-nitrobenzyl chloride and *p*-nitrophenethyl bromide, all substituted aliphatic halides, condensed easily with the sodium salt of 6-methyl-2-thiouracil forming the corresponding mercapto derivatives.

The attempted preparation of 2-(*p*-aminobenzylmercapto)-4-hydroxy-6-methylpyrimidine and 2-(*p*-aminophenethylmercapto)-4-hydroxy-6-methylpyrimidine by the catalytic reduction of their corresponding nitro compounds over Raney nickel catalyst resulted in the formation of resinous polymers containing less than the required amount of sulfur in both cases. The correct amount of hydrogen was absorbed for complete reduction of the nitro groups and then hydrogenation ceased. Johnson and Bailey[9] report that 2-ethylmercapto-4-hydroxy-5-ethyl-6-methylpyrimidine slowly reacts with aniline in ethanolic solution forming 2-anilino-4-hydroxy-5-ethyl-6-methylpyrimidine. It appears probable, therefore,

(8) Jackman, Bergman and Archer, THIS JOURNAL, **70**, 497 (1948).

(9) Johnson and Bailey, *ibid.*, **35**, 1010 (1913).

that the desired aminoaralkylmercaptouracils were first formed on reduction, but later polymerized forming the anilino linkage with adjacent molecules to some extent.

The pharmacological results are to be published elsewhere, and the authors are grateful to Parke, Davis and Company for arranging for the tests.

Experimental

1-Diethylamino-4-carbethoxyhexanone-5.—Sodio ethyl acetoacetate, 0.22 mole, was prepared in 80 ml. of absolute ethanol, and the mixture was gently refluxed while 30 g. (0.2 mole) of γ-diethylaminopropyl chloride was added dropwise over a two-hour period. After six hours of refluxing it was cooled, and filtered free of 10.6 g. of sodium chloride (11.6 g. theoretical).

After the bulk of the ethanol was distilled from the filtrate, the residue was poured into water and extracted with ether. From the aqueous layer considerable polymeric gum, likely arising from quaternization of the γ-diethylaminopropyl chloride, was obtained on evaporation. After drying the ether extract and evaporating the solvent, the residue was distilled through a ten-inch Vigreux column. The principal fraction amounted to 23 g. boiling at 116–129° (1 mm.). On refractionation 17.8 g. (36.5%) of product was collected at 107–109° (0.5 mm.): $n^{20}D$ 1.4514; d^{20}_4 0.956; $M^{20}D$ calcd. 69.06 (keto) 70.10 (enol); $M^{20}D$ obs. 69.0.

On another 0.35-mole run using freshly distilled γ-diethylaminopropyl chloride about 60% of it was added all at once to the refluxing sodio acetoacetic ester solution, and two hours later the remainder was added. After twenty hours of refluxing, the mixture was worked up as before. The residue on distillation gave 53.6 g. (63%) of clear, colorless product at 100–107° (largely at 104–105°) (0.4 mm.): $n^{20}D$ 1.4509.

Anal. Calcd. for $C_{13}H_{25}O_3N$: N, 5.73. Found: N, 5.57.

1-(γ-Diethylaminopropylmercapto)-3-carbethoxypentanone-4.—γ-Diethylaminopropyl β-chloroethyl sulfide was prepared according to the directions of Gilman and Tolman.[10] From 91 g. (1.17 moles) of β-hydroxyethanethiol and 174.5 g. (1.17 moles) of γ-diethylaminopropyl chloride, 191.5 g. (86%) of γ-diethylaminopropyl β-hydroxyethyl sulfide boiling at 105° (1.1 mm.) was obtained. Some physical constants which have not been determined heretofore are: $n^{20}D$ 1.4957; d^{20}_4 0.9830; M_D calcd. 57.3, found 56.8. This was converted to the corresponding chloro compound with thionyl chloride giving 53.5 g. (57%) of product boiling at 84–95° (0.3–0.4 mm.) (bath 112–132°). The constants, which have not been determined heretofore, are: $n^{20}D$ 1.4890; d^{20}_4 1.000; $M^{20}D$ calcd. 60.7, found 60.5. It was conveniently stored as its hydrochloride and recovered as the free base, just prior to use. The freshly distilled γ-diethylaminopropyl β-chloroethyl sulfide, 22.6 g. (0.108 mole) was added dropwise with stirring over a five-hour period to a refluxing solution of 0.12 mole of sodio ethyl acetoacetate in absolute ethanol. Upon working up the product and two fractionations 11 g. (33.5%) of the desired β-oxo ester was obtained boiling at 147–150° (0.4 mm.): $n^{20}D$ 1.4811; d^{20}_4 1.005; $M^{20}D$ calcd. 85.2 (keto), 86.3 (enol), found 86.0.

Anal. Calcd. for $C_{18}H_{29}O_3NS$: S, 10.6. Found: S, 10.8.

Ethyl Picolinoylacetate.—This ester was prepared according to the method of Gilman, Tolman and Massie,[11] who did not, however, isolate the product but hydrolyzed it directly to the ketone *in situ*.

To 13.8 g. (0.6 atom) of sodium sand in 550 ml. dry benzene, 27.6 g. (0.6 mole) of absolute ethanol was added dropwise at such a rate as to promote gentle reflux until all the sodium had reacted. Then a mixture of 60.4 g. (0.4 mole) of ethyl picolinate[12] and 70.4 g. (0.8 mole) of dry ethyl acetate was slowly run into the refluxing suspension. After the addition was complete, the thick sludge was filtered. The precipitate was dissolved in water, treated with an excess of acetic acid, and the liberated ester extracted with ether, dried, and distilled. One portion weighing 24.4 g. was collected at 115–120° (0.4 mm.), $n^{20}D$ 1.5181, and another weighing 29.9 g. at 122–124° (0.5 mm.), $n^{20}D$ 1.5184, d^{20}_4 1.1639, M_D obs. 50.37; M_D calcd. 50.37.[13] Both portions were red when first collected, but soon changed to a straw color on standing; total yield, 54.3 g. (70%).

The identity of the product was established by refluxing a 0.01-mole portion with an equivalent of phenylhydrazine in 10 ml. of ethanol containing a few drops of acetic acid as a catalyst. On cooling, yellow needles of 1-phenyl-3-(α-pyridyl)-pyrazolone-5 melting at 177–178° were obtained: yield, 2 g. (85%) (reported,[3] 179°).

Ethyl Nicotinate.—One hundred grams (0.813 mole) of nicotinic acid was warmed on the steam-bath with a mixture of 250 ml. ethanol and 125 ml. concd. sulfuric acid until all the solid dissolved. After cooling the mixture was poured into 2 kg. of cracked ice and 350 g. of potassium carbonate, then filtered. The filtrate was saturated with sodium carbonate and extracted with ether. On evaporation of the ether the residue yielded on distillation, 88 g. (72%) of colorless, liquid ester boiling at 107–108° (16 mm.).

Ethyl Nicotinoylacetate.—A suspension of 0.75 mole of sodium ethoxide was prepared in 690 ml. of benzene in the manner described above. To this a mixture of 88 g. (1.0 mole) of anhydrous ethyl acetate and 75.5 g. (0.5 mole) of ethyl nicotinate was added slowly under reflux. After twelve hours of refluxing the liquid became clear. The benzene was distilled off on the steam-bath and the residual gum hydrolyzed with an excess of dilute acetic acid. After adding an excess of potassium carbonate, the ester was extracted with ether, dried and distilled. The product was collected as 64.5 g. (67%) of pale, slightly straw-colored oil boiling at 121–123° (0.4 mm.) (reported, by other modifications of the Claisen condensation: 37%[4] as the hydrochloride, and 58%[5]).

Ethyl Isonicotinate.—Isonicotinic acid was prepared by oxidizing 200 g. (2.15 mole) of γ-picoline (technical grade) in 3 l. of water with a total of 680 g. (4.30 mole) of potassium permanganate added portionwise (the reaction easily becomes violent.) A yield of 155 g. (59%) of pure acid was obtained from the acidified filtrate without reworking the mother liquors.

One hundred and forty grams (1.14 moles) of isonicotinic acid suspended in 980 ml. of absolute ethanol was cooled to 0° while dry hydrogen chloride was bubbled in until the solution was saturated. Then with the gas still being slowly passed in, it was refluxed until the solid all dissolved. The excess ethanol was removed under reduced pressure, the solid dissolved in water, cooled and treated with an excess of saturated sodium carbonate solution, filtered and extracted with ether. On distillation 105.5 g. (61.4%) of clear, colorless ester was obtained boiling at 105–108° (16–17 mm.) (reported[4]: 30% yield by the method of Camps).

Ethyl Isonicotinoylacetate.—The technique used in this preparation was parallel to that used in synthesizing the β-pyridoyl isomer. From 0.5 mole of ethyl isonicotinate 66.4 g. (69%) was obtained boiling at 118–120° (0.4 mm.), m. p. 53–55° (reported[5]: m. p. 54°, in 85% yield by another technique).

(10) Gilman and Tolman, THIS JOURNAL, 67, 1847 (1945).

(11) Gilman, Tolman and Massie, *ibid.*, 68, 2399 (1946).

(12) Kindly supplied by S. P. Massie of these laboratories.

(13) The calculated value will vary a great deal depending on the numerical contribution to the total molecular refraction assigned to the pyridine moeity of the molecule. The calculated value shown was obtained using the atomic and structural factors given in Gilman, "Organic Chemistry," Vol. II, 2nd ed., John Wiley and Sons, New York, 1943, p. 1751, and considering the contributions of the three double bonds in pyridine as equal to $3 \times 1.73 = 5.19$. The close agreement is undoubtedly fortuitous under the circumstances.

Ethyl *p*-Anisoylacetate.—To sodamide prepared from 9.2 g. (0.4 atom) of sodium in 250 ml. of liquid ammonia 30 g. (0.2 mole) of *p*-methoxyacetophenone dissolved in 100 ml. of dry ether was added with vigorous stirring. The excess ammonia was evaporated off and replaced with ether. Under reflux 47.2 g. (0.4 mole) of ethyl carbonate was then added. After stirring the fluid grayish black suspension under reflux for five hours, a semi-solid mass resulted which was hydrolyzed with acetic acid and extracted with ether. After drying and evaporating the solvent, the residue was distilled with some decomposition giving 11.9 g. (26.8%) of clear, viscous oil at 155–158° (0.6–0.7 mm.) (reported,[14] boiling point 180–190° (10–12 mm.) with decomposition, prepared by another method).

The identity of the ester, prepared by this method for the first time, was established by refluxing a small portion in ethanol with hydroxylamine hydrochloride. Long, slender, white needles of 3-(*p*-methoxyphenyl)-isoxazolone-5 were obtained melting at 140–141° (reported,[15] 143°).

Ethyl β-(2-Thienyl)-β-oxopropionate.—According to the procedure of Levine and Hauser,[12] 0.4 mole of 2-acetothienone was carbethoxylated in the presence of sodamide. A yield of 33.3 g. (84%) of viscous, oily ester distilling at 121–123° (0.4–0.5 mm.) was obtained (reported,[16] 48% yield boiling at 150–153° (5 mm.)).

6-(α-Pyridyl)-2-thiouracil. Procedure A.—The procedure used was substantially that of Anderson, *et al.*[2] Thiourea, 3.8 g. (0.05 mole), and 8.95 g. (0.05 mole) of ethyl picolinoylacetate were added to 0.1 mole of sodium ethoxide in ethanol. Almost immediately a precipitate began to form. After refluxing overnight, the solvent was removed under reduced pressure, the residue taken up in water, filtered, and acidified with acetic acid. The precipitate was filtered off, dried and recrystallized from 200 ml. of glacial acetic acid. Three grams (29%) of hard, well formed crystals with a faint greenish cast was obtained. They melted with slight decomposition at 291–294°. The procedure followed in preparing the other 6-substituted-2-thiouracils was analogous.

2-(γ-Diethylaminopropylmercapto)-4-hydroxy-6-methylpyrimidine. Procedure B.—A suspension of the sodium salt of 6-methyl-2-thiouracil was prepared by digesting 7.1 g. (0.05 mole) of the thiouracil in a solution of 0.05 mole of sodium ethoxide in 50 ml. of ethanol at reflux temperature for two hours. Then 7.5 g. (0.05 mole) of γ-diethylaminopropyl chloride in 25 ml. of ethanol was added, and the mixture was stirred under reflux for six hours. The cooled mixture was filtered free of sodium chloride and the solvent evaporated. On distillation 10.5 g. (82.4%) of a colorless, very viscous oil, almost a glass, was obtained boiling at 183–188° (0.4 mm.). It was very soluble in ethanol, insoluble in water and ligroin, and sparingly soluble in ether. We were not successful in obtaining a crystalline hydrochloride.

The other two compounds prepared by this method (procedure B) were themselves insoluble in ethanol; consequently, the reaction mixture slurry was exhaustively washed with water to remove inorganic substituents and the residue recrystallized to constant melting point (see Table I).

Catalytic Reduction of 2-(*p*-Nitrobenzylmercapto)-4-hydroxy-6-methylpyrimidine and its Next Higher Homolog.—Ten grams (0.036 mole) of the former compound suspended in 200 ml. dioxane with 2–3 g. Raney nickel catalyst was shaken under 4 atm. pressure of hydrogen. The calculated amount of hydrogen for complete reduction of the nitro group was absorbed in five hours, then the uptake of hydrogen ceased. After filtering and removing the solvent under reduced pressure, a hard, red glass softening gradually above 110° was obtained. It was ground to a resinous, yellow powder and dried *in vacuo* at 110° for analysis.

Anal. Calcd. for $C_{12}H_{13}ON_3S$: S, 12.69. Found: S, 10.83.

From a similar treatment of the next higher homolog, the phenethyl derivative, an orange vitreous mass, insoluble in ether and ethanol, was obtained which could not be crystallized. It melted *ca.* 55–70°. This polymeric material also gave a low analysis for sulfur.

Anal. Calcd. for $C_{13}H_{15}ON_3S$: S, 12.27. Found: S, 11.17.

(14) Wahl and Silberzweig, *Bull. soc. chim.*, [4] **11**, 27 (1912).
(15) Wahl, *Compt. rend.*, **148**, 353 (1909).
(16) Levine and Hauser, THIS JOURNAL, **66**, 1769 (1944).

Summary

1. Some new derivatives of 2-thiouracil have been prepared for evaluation as antithyroid agents.

2. Two new β-oxo esters have been isolated and improved techniques for the preparation of some others and their precursory starting materials have been described.

3. Catalytic reduction of 2-(*p*-nitrobenzylmercapto)-4-hydroxy-6-methylpyrimidine and its next higher homolog was found to initiate a complex reaction yielding polymeric substances.

AMES, IOWA RECEIVED MAY 7, 1948

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES OF THE UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. XXII. Piperazinium Salts for Utilization in Identification of Organic Acids

BY M. PRIGOT AND C. B. POLLARD

In previous papers[1,2] from this Laboratory certain piperazinium salts were reported for utilization in identification of organic acids. The present paper describes an improved method of preparation, and data concerning thirty-six new piperazinium salts are shown in Table I.

Experimental

The respective acid was dissolved in anhydrous ether or propanol-2 in a Waring blendor. The calculated amount of piperazine was added as 1 *M* piperazine in propanol-2 during vigorous stirring. The precipitate was suction filtered, added to fresh ether or propanol-2, stirred again in a Waring blendor, refiltered and dried in a desiccator over phosphorus pentoxide before physical constants were determined. For purposes of qualitative analysis plate drying is usually sufficient. Acids which were quite insoluble in ether or propanol-2 were dissolved in water before addition of piperazine. This necessitated evaporation on a steam-bath to recover the piperazinium salts.

Melting points are corrected and were determined by use of a bronze block, preheated to within 5° of the m. p.

Neutral equivalents were determined by dissolving the salt in 50% aqueous propanol-2 and titrating with 0.1 *N*

(1) Pollard and Adelson, THIS JOURNAL, **56**, 150 (1934).
(2) Pollard, Adelson and Bain, *ibid.*, **56**, 1759 (1934).