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.

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.

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(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).

[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).

TABLE I

DATA CONCERNING PIPERAZINIUM SALTS DERIVED FROM VARIOUS ORGANIC ACIDS

Acids, common name of acid	Yield, %	Piperazinium salts: Melting point, °C. cor.	Neutral equivalents Calcd.	Found	Nitrogen, % Calcd.	Found
o-Benzoylbenzoic	78	186.2–186.6	287	289	4.88	4.79
o-Bromobenzoic	90	227–230 dec.	244	241	5.74	5.87
m-Bromobenzoic	74	169–171	244	250	5.74	5.52
p-Bromobenzoic	49	224–226	244	240	5.74	5.75
α-Bromopropionic	73	195 dec.	196	192	7.14	6.96
Dichloroacetic[b]	62	181 dec.	343.9	339.7	8.15	8.22
n-Capric	49	92.5–93.5	215	219	6.50	6.51
n-Caprylic	32	97.5–98.0	187	184	7.48	7.51
o-Chlorobenzoic	81	217–218 dec.	200	194	7.02	6.93
p-Chlorobenzoic	67	219–220 dec.	200	199	7.02	6.76
trans-Cinnamic	92	206 dec.	191	190	7.33	7.46
Citric	100	141–142	139	137	10.1	10.4
Ethoxyacetic	73	120–121	147	145	9.55	9.60
p-Ethoxybenzoic	76	176.2–177.0 dec.	209	211	6.70	6.10
Fumaric	98	240 dec.	101	105	13.9	13.5
α-Furoic	94	234–236 dec.	155	160	9.03	8.84
Gallic	84	209.0–209.7 dec.	213	[a]	6.57	6.57
Hippuric	82	182–184 dec.	222	222	12.6	12.0
Lauric	77	92.0–92.5	243	243	5.76	5.86
Maleic	92	148	101	102	13.85	13.43
Methoxyacetic	80	155.7–156.4	133	132	10.52	10.41
o-Methoxybenzoic	92	190.4–191.4	195	196	7.18	7.03
m-Methoxybenzoic	89	136.9–138.5 dec.	195	202	7.18	7.26
α-Naphthoic	48	131.5–139.0 dec.	215	216	6.51	6.45
β-Naphthoic	89	194.0–195.0 dec.	215	217	6.51	6.46
p-Nitrocinnamic	90	247.9–248.7 dec.	232	232	11.86	11.59
p-Nitrophenylacetic	96	205.5–205.9 dec.	224	225	12.49	12.39
4-Nitrophthalic	96	201.5–204.5 dec.	149	149	14.14	13.7
Pelargonic	60	95.1–96.2	201	198	7.03	6.96
Phenoxyacetic	84	183.7–184.2 dec.	195	195	7.18	6.94
o-Phthalic[b]	91	187–188	139	139	6.69	6.73
Isophthalic	77	251.7–252.2 dec.	126	126	11.2	11.1
Terephthalic	52	Dec. above 350	126	127	11.2	10.9
d-Tartaric	86	248–254	118	117	11.9	11.2
meso-Tartaric	87	140–141	118	119	11.9	11.5
p-Toluic	79	203.0–203.3	179	181	7.82	7.61

[a] Solution too dark to titrate. [b] Previously prepared by Pollard, Adelson and Hampton, but not reported.

sodium hydroxide using either thymolphthalein or Orange II as indicator.

By the method employed the following acids failed to give salts which are of practical value for qualitative organic analysis: α-bromo-*n*-butyric, anthraquinone-β-sulfonic, barbituric, 2-chloropropionic, 2,5-dichlorobenzenesulfonic, 2,4-dichlorophenoxyacetic, diethylacetic, diphenylacetic, erucic, glycine, *p*-hydroxybenzoic, iodoacetic, itaconic, levulinic, *dl*-methylethylacetic, mucic, 1-naphthol-4-sulfonic, sulfosalicylic, thioglycolic, and trimesic.

Summary

Thirty-six new piperazinium salts which may be utilized for the identification of organic acids are reported.

Twenty organic acids which failed to give suitable derivatives are listed.

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