resulting crystals were digested with ether (30 cc.) at room temperature. The ether-insoluble residue (80 mg.), m.p. 158–159° on recrystallization from ethanol, gave shiny needles of dibromide A, m.p. 157–158°, $[\alpha]^{25}D$ −46° (*c* 1.196); λ_{max}^{alc} 250 mμ (19,500), 355 mμ (86).

Anal. Calcd. for $C_{31}H_{43}O_5NBr_2$ (669.5): C, 55.61; H, 6.47; Br, 23.9. Found: C, 56.59; H, 6.43; Br, 24.1.

The ether extract, was brought to dryness, and the residue was recrystallized from ethanol, yielding 615 mg. of dibromide B (fine needles), m.p. 146–147°, $[\alpha]^{24}D$ −68° (*c* 1.39); λ_{max}^{alc} 250 mμ (17,000), 355 mμ (60).

Anal. Calcd. for $C_{31}H_{43}O_5NBr_2$ (669.5): C, 55.61; H, 6.47; Br, 23.9. Found: C, 55.90; H, 6.10; Br, 23.8.

No appreciable changes in rotation were observed with either dibromides when their solutions in chloroform were allowed to stand at room temperature for 6 days.

Dibromide A (40 mg.) was debrominated by refluxing its solution in ethanol (5 cc.) with zinc dust (200 mg.) for one hour. On gradual addition of water needles (27 mg.) deposited which after recrystallization from 50% aqueous ethanol melted at 171–172°, and did not depress the melting point of an authentic sample of diacetyljervine (m.p. 170–171°).

The same result was obtained with dibromide B.

Jervine Dibromide Hydrobromide.—To a solution of jervine (100 mg.) in acetic acid (3 cc.) bromine in the same solvent (15.1 mg./cc.) was added dropwise at intervals over the course of 90 minutes. Addition was stopped when 3.1 cc. had been decolorized. On standing overnight, a crystalline precipitate (51 mg.) separated, which was recrystallized by dissolving it in hot methanol (15 cc.) and concentrating to 3 cc.; needles, m.p. 217–219°, $[\alpha]^{25}D$ −88° (*c* 0.328 in 50% aqueous ethanol); λ_{max}^{alc} 245 mμ (18,300); λ_{max}^{nujol} 3.03, 5.88, 6.17 μ.

Anal. Calcd. for $C_{27}H_{39}O_3NBr_2 \cdot HBr$ (667): Br, 36.0. Found: 34.6.

O-Acetyljervine.—A solution of jervine (500 mg.) in acetic acid (10 cc.) was refluxed for 18 hours. The solvent was removed *in vacuo*, and the dark-red residue was taken up in water. After alkalization with sodium hydroxide the solution was extracted with chloroform, and the extract was washed with water, partially decolorized by treatment with charcoal, and taken to dryness. The crystalline product obtained on the addition of ethanol to the residue (221 mg.) was recrystallized from acetone: needles, m.p. 277–279° $[\alpha]^{27}D$ −138° (*c* 0.54 in absolute ethanol); λ_{max}^{alc} 252 mμ (14,700), 360 mμ (53); λ_{max}^{nujol} 5.79, 5.89, 6.14, 7.98 μ.

Anal. Calcd. for $C_{29}H_{41}O_4N$ (467.7): C, 74.47; H, 8.84; $COCH_3$, 9.20. Found: C, 74.51; H, 8.74; $COCH_3$, 9.5.

On hydrolysis with 5% methanolic potassium hydroxide (refluxing 30 min.) pure jervine, m.p. 241–243°, $[\alpha]^{25}D$ −148° (*c* 1.03 in ethanol), was obtained in almost quantitative yield.

O-Acetyldihydrojervine.—Dihydrojervine was acetylated as described above for jervine. The melting point of the crude product (375 mg., 66% of theory) was 280–282°, and remained unchanged on recrystallization from methanol; $[\alpha]^{24}D$ −100° (*c* 0.948), −86° (*c* 0.548 in absolute ethanol); λ_{max}^{nujol} 5.80, 7.95.

Anal. Calcd. for $C_{29}H_{43}O_4N$ (469.7): C, 74.16; H, 9.23; $COCH_3$, 9.16. Found: C, 74.45; H, 9.10; $COCH_3$, 9.3.

Alkaline hydrolysis yielded pure dihydrojervine, m.p 242–244°, and N-acetylation in methanol diacetyldihydrojervine, m.p. 213–216°, $[\alpha]^{25}D$ −64° (*c* 1.30).

O-Acetyltetrahydrojervine prepared from tetrahydrojervine in the above manner (yield 49%) melted at 250–252° and showed $[\alpha]^{25}D$ −48° (*c* 0.851); λ_{max}^{nujol} 5.80, 7.96 μ.

Anal. Calcd. for $C_{29}H_{45}O_4N$ (471.7): C, 73.83; H, 9.62; $COCH_3$, 9.12. Found: C, 73.72; H, 9.57; $COCH_3$, 9.50.

Alkaline hydrolysis regenerated tetrahydrojervine, m.p. 212–214°.

Cholesterol (500 mg.) when acetylated under the above conditions gave 436 mg. of the pure acetate, m.p. 212–213.5°, by recrystallization of the crude product. With dihydrojervine and tetrahydrojervine shortening of the reflux period to 5 hours resulted in lower yields and less pure products. Attempts to O-acetylate these compounds with acetic acid at room temperature in the presence of catalytic amounts of perchloric acid failed on account of the fact that unacetylated bases (in contrast to their O-acetyl derivatives) form perchlorates insoluble in cold acetic acid, while heating such mixtures results in decomposition.

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Hydrazides of Some Pyridazonyl Substituted Acids

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Hydrazides have been prepared of a group of eighteen aliphatic carboxylic acids each of which contains a 6-pyridazonyl-1-substituent. These hydrazides were prepared by the reaction of hydrazine with the corresponding ethyl esters which in turn were prepared by alkylation of the appropriately substituted 6-pyridazone with bromosubstituted esters. Some of the starting pyridazones are new and their preparation is described. Some of these hydrazides under the condition of our test caused stimulation of the growth of embryonic chick fibroblasts.

As part of our microbiological screening program certain pyridazonyl substituted aliphatic hydrazides were incorporated into tissue cultures using the techniques of Dulbecco.[1,2] There was evidence from preliminary studies that certain compounds in the series could stimulate the growth of embryonic chick fibroblasts. In order to obtain a quantitative measure of cell proliferation in tissue culture the method of Sanford[3] was used. A description of the microbiological procedures and results, with a discussion of the possible therapeutic implications, will be published elsewhere. The present paper describes the synthesis of these hydrazides and of intermediates necessary for their preparation.

In a previous communication[4] we have shown that 6-pyridazone and 3-methyl-6-pyridazone were easily alkylated with α-bromoacetic esters in the presence of sodium ethoxide in ethanol. Using the same general method we have prepared a number of pyridazonyl alkanoic esters by using a variety of bromosubstituted esters to effect the

(1) R. Dulbecco, *Proc. Nat. Acad. Sci.*, **38**, 747 (1952).

(2) R. Dulbecco and M. Vogt, *J. Exper. Medicine*, **99**, 167 (1954).

(3) K. K. Sanford, W. R. Earle, V. J. Evans, H. K. Waltz and J. E. Shannon, *J. Natl. Cancer Inst.*, **11**, 773 (1951).

(4) John A. King and Freeman H. McMillan, THIS JOURNAL, **74**, 3222 (1952).

alkylation of variously substituted 6-pyridazones.

The pyridazones which we have used are 6-pyridazone (I), 3-methyl-6-pyridazone (II), 5-methyl-6-pyridazone (III), 3,4-dimethyl-6-pyridazone (IV), 3,5-dimethyl-6-pyridazone (V), 3,4,5-trimethyl-6-pyridazone (VI), 3-ethyl-6-pyridazone (VII), 3-phenyl-6-pyridazone (VIII) and 3-(*p*-bromophenyl)-6-pyridazone (IX). Compounds I, II, VIII and IX are known and were prepared as reported in the literature. Compound IV has been prepared by Schmidt and Druey[5] by an ingenious condensation of diacetyl with cyanoacethydrazide followed by hydrolysis and decarboxylation; we have prepared this compound by an older procedure, *viz.* condensation of β-methyllevulinic acid with hydrazine followed by dehydrogenation with bromine of the resulting dihydropyridazone.[5a] Compound V was reported by Ajello and Cusmano[6] prepared from hydrazine and α-methyl-β-acetylacrylic acid; we have used the same method as for IV using α-methyllevulinic acid. Compound VI has not been described although its use is alluded to.[7] We have prepared this compound from α,β-dimethyllevulinic acid by the same procedure used to prepare IV. Compound VII was isolated only as its hydrobromide salt by Grundmann[8] who prepared the compound by the condensation of homolevulinic acid with hydrazine followed by dehydrogenation with bromine. We have used the same general procedure and were successful in isolating and characterizing the free pyridazone. Compound III is new and has been prepared by the condensation of α-keto-α′-methylglutaric acid with hydrazine followed by dehydrogenation with bromine and subsequent decarboxylation.

A variety of bromoesters was used to effect the alkylation of 3-methyl-6-pyridazone: (1) in addition to ethyl bromoacetate, ethyl α-bromopropionate and ethyl α-bromoisobutyrate previously reported[2] we have used ethyl α-bromo-*n*-butyrate, ethyl α-bromo-*n*-valerate, ethyl α-bromocaproate, ethyl α-bromo-*n*-heptanoate and ethyl α-bromophenylacetate to effect the alkylation of 3-methyl-6-pyridazone giving a variety of α-substituted 3-methyl-6-pyridazonyl-1-acetates; (2) in order to inject a longer carbon chain between the ester group and the pyridazone ring we have also used ethyl β-bromopropionate and ethyl ω-bromoundecanoate to effect the alkylation. No particular difficulty was encountered in carrying out any of the above alkylations; however, it was noted that when ethyl β-bromopropionate was used the reaction mixture had a very strong odor of ethyl acrylate. This tendency toward dehydrohalogenation was even more pronounced in the case of ethyl β-bromoisobutyrate; in several attempts to use this ester to effect the alkylation of 3-methyl-6-pyridazone no alkylation was observed and ethyl methacrylate was formed. We further observed that when 3-methyl-6-pyridazone and ethyl acrylate were mixed in ethanol solution containing a trace of sodium ethoxide a very mildly exothermic reaction took place and ethyl β-(3-methyl-6-pyridazonyl-1)-propionate was formed; under the same conditions the pyridazone did not add to ethyl methacrylate.

The remaining pyridazones were alkylated only with ethyl bromoacetate.

The hydrazides were all prepared by the reaction of hydrazine with the corresponding esters, usually in refluxing ethanol, and in general good yields were obtained. In a few instances, however, where there was steric hindrance to the reaction, *e.g.*, the isobutyrate, or in the case of higher molecular weight compounds such as the undecanoate, the hydrazine did not react with the esters under these conditions and it was necessary to use *n*-propyl alcohol as solvent either at reflux or at higher temperature in pressure bottles.

Experimental[9,10]

3-Carboxy-5-methyl-6-pyridazone.—A solution of 3-carboxy-5-methyl-4,5-dihydro-6-pyridazone[11] (32 g., 0.205 mole) in 200 ml. of glacial acetic acid was heated to boiling and, with stirring, bromine (33.6 g., 0.21 mole) was added dropwise. After the addition was complete the mixture was heated at reflux for 15 minutes and then diluted with 200 ml. of water and evaporated to dryness under vacuum. The residue was crystallized from 1500 ml. of water giving 28.0 g. (89% yield) of crystals melting at 275° dec.; additional crystallizations did not raise this melting point.

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.75; H, 3.92; N, 18.18. Found: C, 46.79; H, 4.16; N, 17.98.

5-Methyl-6-pyridazone.—3-Carboxy-5-methyl-6-pyridazone (27 g., 0.175 mole) was heated at atmospheric pressure until the material was all melted after which it was distilled at 100 mm. pressure giving 16 g. of distillate; this distillate was crystallized from 350 ml. of benzene giving 10 g. (52% yield) of material melting at 158–159°. Recrystallization did not raise this melting point.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.53; H, 5.49; N, 25.44. Found: C, 54.79; H, 5.29; N, 25.23.

3,4-Dimethyl-4,5-dihydro-6-pyridazone.—A solution of β-methyllevulinic acid[12] (13.0 g., 0.10 mole) in 25 ml. of ethanol was mixed with a solution of hydrazine hydrate (5.0 g., 0.10 mole) in 25 ml. of ethanol. The resulting solution, which got quite warm, was evaporated to dryness under vacuum leaving 12.6 g. (quantitative yield) of crystalline material which melted at 98–108°. A small portion after two recrystallizations from petroleum ether (b.p. 85–100°) melted at 111.5–112.5°.

Anal. Calcd. for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.21. Found: C, 57.31; H, 7.83; N, 22.01.

3,4-Dimethyl-6-pyridazone.—By the bromine dehydrogenation procedure described above 3,4-dimethyl-4,5-dihydro-6-pyridazone gave, after crystallization from water, an 81% yield of 3,4-dimethyl-6-pyridazone melting at 225–228°. A small sample after recrystallization from benzene melted at 232–233°. Schmidt and Druey[5] reported that this material prepared by a different route melted at 221–222°.

Anal. Calcd. for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.15; H, 6.65; N, 22.33.

3,5-Dimethyl-4,5-dihydro-6-pyridazone.—As described above for the 3,4-dimethyl isomer, α-methyllevulinic acid and hydrazine in ethanol gave a quantitative yield of 3,5-dimethyl-4,5-dihydro-6-pyridazone melting at 59.5–62.5°. A small portion after recrystallization from petroleum ether (b.p. 85–100°) melted at 62.5–63.5°.

Anal. Calcd. for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.21. Found: C, 57.11; H, 8.24; N, 22.23.

(5) P. Schmidt and J. Druey, *Helv. Chim. Acta*, **37**, 1467 (1954).

(5a) Note added in proof.—Since this manuscript was written, this reaction has been reported by R. H. Horning and E. D. Amstutz, *J. Org. Chem.*, **20**, 707 (1955).

(6) T. Ajello and S. Cusmano, *Gass. chim. ital.*, **70**, 765 (1940).

(7) P. S. Winnek and R. O. Roblin, Jr., U. S. Patent 2,371,115 (March 6, 1945).

(8) C. Grundmann, *Ber.*, **81**, 1 (1948).

(9) Boiling points and melting points are uncorrected.

(10) Microanalyses were carried out by Mr. Louis Dorfman and Miss Lorelinde Einstein.

(11) E. E. Blaise and H. Gault, *Bull. soc. chim.*, [4] **9**, 451 (1911).

(12) E. E. Blaise, *ibid.*, [3] **23**, 920 (1900).

3,5-Dimethyl-6-pyridazone.—A solution of 3,5-dimethyl-4,5-dihydro-6-pyridazone (10.0 g., 0.079 mole) in 75 ml. of glacial acetic acid was heated to boiling and bromine (12.9 g., 0.079 mole) was added dropwise to the stirred solution after which the mixture was heated at reflux for 15 minutes. The reaction mixture was diluted with 75 ml. of water and evaporated to dryness under vacuum. The residue was crystallized from 10 ml. of water giving 3.0 g. of material which melted at 240° dec.; this material, which after recrystallization from a little methanol melted at 255° dec., gave a strong ionic halogen test and was the hydrobromide of 3,5-dimethyl-6-pyridazone.

Anal. Calcd. for $C_6H_9BrN_2O$: C, 35.14; H, 4.42; N, 13.66; Br, 38.97. Found: C, 35.36; H, 4.87; N, 13.71; Br, 39.04.

The original water mother liquor was neutralized with sodium hydroxide solution and the neutral solution was evaporated to dryness under vacuum. The residue was boiled with 30 ml. of benzene and the resulting suspension was filtered. The chilled benzene filtrate gave 6.0 g. (61% yield) of 3,5-dimethyl-6-pyridazone melting at 126–128°. A small sample after recrystallization from petroleum ether (b.p. 85–100°) melted at 130–131°. Ajello and Cusmano[4] reported that this material, prepared by another method, melted at 125°.

Anal. Calcd. for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.18; H, 6.60; N, 22.50.

3,4,5-Trimethyl-4,5-dihydro-6-pyridazone.—α,β-Dimethyllevulinic acid[13] (14.4 g., 0.10 mole) and hydrazine hydrate (5.0 g., 0.10 mole) were mixed in ethanol and the solution was evaporated to dryness under vacuum. The viscous residue was distilled giving a crystalline distillate boiling at 79° (0.1 mm.) which was recrystallized from petroleum ether (b.p. 60–70°) giving 8.5 g. (61% yield) of material melting at 85–86°.

Anal. Calcd. for $C_7H_{12}N_2O$: C, 59.97; H, 8.63; N, 19.98. Found: C, 60.27; H, 8.66; N, 19.87.

3,4,5-Trimethyl-6-pyridazone.—A solution of 3,4,5-trimethyl-4,5-dihydro-6-pyridazone (57 g., 0.41 mole) in 250 ml. of glacial acetic acid was heated to boiling and bromine (65.5 g., 0.41 mole) was added dropwise with stirring to the solution. After the addition was complete the solution was heated at reflux for 15 minutes after which the acetic acid was distilled off under vacuum. The residue was dissolved in 200 ml. of water and this solution was brought to *p*H 7 with sodium hydroxide solution. An orange-yellow solid precipitated which weighed 42 g. (74% yield) and melted at 238–245°. A small sample after recrystallization from ethyl acetate and again from water melted at 249.5–250°.

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.74; H, 7.10; N, 20.14.

3-Ethyl-6-pyridazone.—A solution of 3-ethyl-4,5-dihydro-6-pyridazone[6] (40.5 g., 0.322 mole) in 160 ml. of glacial acetic acid was heated to boiling and the solution was treated dropwise with bromine (52 g., 0.325 mole). After the addition was complete the mixture was heated under reflux for 15 minutes. The reaction mixture was then diluted with 100 ml. of water and evaporated to dryness under vacuum. The residue was dissolved in 200 ml. of water and this solution was neutralized with sodium hydroxide solution after which the solution was evaporated to dryness under vacuum. The residue was boiled with 250 ml. of absolute ethanol and the sodium bromide removed by filtration. The alcohol was evaporated from the filtrate and the residue was distilled giving 17 g. (42.5%) of material which slowly crystallized. A small sample after recrystallization from petroleum ether (b.p. 60–70°) melted at 95°.

Anal. Calcd. for $C_6H_8N_2O$: C, 58.05; H, 6.49; N, 22.57. Found: C, 57.92; H, 6.56; N, 22.43.

Preparation of Esters. Ethyl β-(3-Methyl-6-pyridazonyl-1)-propionate.—To a solution of sodium (12.7 g., 0.55 mole) in 450 ml. of absolute ethanol there was added 3-methyl-6-pyridazone (60.5 g., 0.55 mole). This solution was stirred at less than 20° while ethyl β-bromopropionate (100 g., 0.55 mole) was added dropwise. When the addition was complete the reaction mixture was heated under reflux for three hours after which it was cooled and filtered to remove sodium bromide. The ethanol was removed from the filtrate by distillation under vacuum and the residue was taken up in 250 ml. of benzene. The benzene solution was washed with three 100-ml. portions of water to remove residual sodium bromide and unreacted pyridazone after which the benzene was stripped off under vacuum and the residue was distilled giving 53.5 g. (46.5% yield) of material boiling at 124° (0.5 mm.).

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.31; H, 6.80; N, 13.20.

Ethyl ω-(3-Methyl-6-pyridazonyl-1)-undecanoate.—Similarly when ethyl ω-bromoundecanoate[14] was used to alkylate 3-methyl-6-pyridazone there was obtained ethyl ω-(3-methyl-6-pyridazonyl-1)-undecanoate in 47.5% yield boiling at 166–170° (0.04 mm.).

Anal. Calcd. for $C_{15}H_{30}N_2O_3$: C, 67.05; H, 9.38; N, 8.69. Found: C, 67.06; H, 9.52; N, 8.75.

Ethyl α-(3-Methyl-6-pyridazonyl-1)-*n*-butyrate.—By the same procedure ethyl α-bromo-*n*-butyrate and 3-methyl-6-pyridazone gave ethyl α-(3-methyl-6-pyridazonyl-1)-*n*-butyrate in 79% yield boiling at 92° (0.05 mm.).

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.76; H, 7.33; N, 12.55.

Ethyl α-(3-Methyl-6-pyridazonyl-1)-*n*-valerate.—This ester was obtained from ethyl α-bromo-*n*-valerate in 82.5% yield boiling at 111° (0.15 mm.).

Anal. Calcd. for $C_{12}H_{18}N_2O_3$: C, 60.48; H, 7.61; N, 11.76. Found: C, 60.39; H, 7.76; N, 11.88.

Ethyl α-(3-Methyl-6-pyridazonyl-1)-caproate.—This ester was obtained from ethyl α-bromo-*n*-hexanoate in 79.5% yield boiling at 117° (0.3 mm.).

Anal. Calcd. for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.11. Found: C, 61.85; H, 8.08; N, 11.19.

Ethyl α-(3-Methyl-6-pyridazonyl-1)-*n*-heptanoate.—This ester was prepared from ethyl α-bromo-*n*-heptanoate in 63% yield boiling at 129° (0.2 mm.).

Anal. Calcd. for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N, 10.52. Found: C, 63.25; H, 8.46; N, 10.61.

Ethyl α-Phenyl-α-(3-methyl-6-pyridazonyl-1)-acetate.—To a solution of sodium (15.5 g., 0.675 mole) in 700 ml. of absolute ethanol there was added with stirring 3-methyl-6-pyridazone (74.5 g., 0.675 mole). The reaction mixture was cooled to less than 10° while ethyl α-bromophenylacetate (164 g., 0.675 mole) was added dropwise. When the addition was complete, the reaction mixture was heated at 50° for one hour. The sodium bromide was filtered off while the reaction mixture was still hot. The filtrate was concentrated to 500 ml. under vacuum, heated to the boiling point and filtered. The chilled filtrate yielded crystals (69.5 g., 38%) which melted at 119–122°. A small sample, recrystallized from absolute ethanol, melted at 121–123°.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.15; H, 5.92; N, 10.29. Found: C, 66.17; H, 5.94; N, 10.03.

Ethyl (5-Methyl-6-pyridazonyl-1)-acetate.—To a solution of sodium (6.9 g., 0.3 mole) in 300 ml. of absolute ethanol there was added 5-methyl-6-pyridazone (33 g., 0.3 mole). This solution was stirred at less than 10° while ethyl α-bromoacetate (50 g., 0.3 mole) was added dropwise. After the addition was complete, the reaction mixture was heated under reflux for one hour after which it was cooled and filtered to remove sodium bromide. The filtrate was evaporated to dryness under vacuum and the residue was dissolved in 250 ml. of benzene. The benzene solution was washed with two 100-ml. portions of water and was dried over anhydrous sodium sulfate. The benzene was evaporated under vacuum and the residue was crystallized from 300 ml. of petroleum ether (b.p. 85–100°). The product weighed 24 g. (41% yield) and melted at 75–76°. Recrystallization did not raise its melting point.

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.21; H, 6.32; N, 14.20.

Ethyl (3,5-Dimethyl-6-pyridazonyl-1)-acetate.—Similarly 3,5-dimethyl-6-pyridazone and ethyl bromoacetate gave this ester in 40% yield melting at 107–108°.

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, N, 13.33. Found: C, 57.17; H, 6.78; N, 13.16.

Ethyl (3,4-Dimethyl-6-pyridazonyl-1)-acetate.—By the procedure used to prepare ethyl β-(3-methyl-6-pyridazonyl-1)-propionate, 3,4-dimethyl-6-pyridazone and ethyl bromo-

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(14) J. Walker and J. S. Lumsden, *J. Chem. Soc.*, **79**, 1191 (1901).

Table I

Hydrazides

Name of hydrazide	Empirical formula	M.p., °C.	Yield, %	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
6-Pyridazonyl-1-acetic	$C_6H_8N_4O_2$	213–216	72	42.85	4.79	33.32	42.98	4.84	33.20
3-Methyl-6-pyridazonyl-1-acetic	$C_7H_{10}N_4O_2$	199–200	88	46.15	5.53	30.75	46.24	5.56	30.88
β-(3-Methyl-6-pyridazonyl-1)-propionic	$C_8H_{12}N_4O_2$	151–153	80	48.97	6.17	28.56	49.06	6.10	28.46
ω-(3-Methyl-6-pyridazonyl-1)-undecanoic[a]	$C_{16}H_{28}N_4O_2$	85–87	18	62.31	9.15	18.17	62.43	9.26	18.05
α-(3-Methyl-6-pyridazonyl-1)-propionic	$C_8H_{12}N_4O_2$	134.5–135	65	48.97	6.17	28.56	48.82	6.16	28.46
α-(3-Methyl-6-pyridazonyl-1)-butyric	$C_9H_{14}N_4O_2$	125.5–127	77	51.42	6.71	26.65	51.56	6.90	26.71
α-(3-Methyl-6-pyridazonyl-1)-valeric	$C_{10}H_{16}N_4O_2$	112–115	44	53.55	7.19	24.98	53.52	7.31	24.85
α-(3-Methyl-6-pyridazonyl-1)-caproic	$C_{11}H_{18}N_4O_2$	122–124	49	55.44	7.61	23.51	55.61	7.84	23.65
α-(3-Methyl-6-pyridazonyl-1)-heptanoic	$C_{12}H_{20}N_4O_2$	108–109	53	57.12	7.99	22.21	57.29	8.10	22.11
α-Phenyl-α-(3-methyl-6-pyridazonyl-1)-acetic[b]	$C_{13}H_{14}N_4O_2$	191–192	79	60.45	5.46	21.69	60.32	5.29	21.66
α-(3-Methyl-6-pyridazonyl-1)-isobutyric[c]	$C_9H_{14}N_4O_2$	165–166	22	51.42	6.71	26.65	51.37	6.78	26.54
5-Methyl-6-pyridazonyl-1-acetic	$C_7H_{10}N_4O_2$	203–204.5	73	46.15	5.53	30.76	46.22	5.40	30.64
3,5-Dimethyl-6-pyridazonyl-1-acetic	$C_8H_{12}N_4O_2$	194–196	44	48.97	6.17	28.56	48.97	6.25	28.53
3,4-Dimethyl-6-pyridazonyl-1-acetic	$C_8H_{12}N_4O_2$	205–206	78	48.97	6.17	28.56	48.78	6.38	28.60
3,4,5-Trimethyl-6-pyridazonyl-1-acetic	$C_9H_{14}N_4O_2$	217–221	79	51.42	6.71	26.65	51.34	6.59	26.76
3-Ethyl-6-pyridazonyl-1-acetic	$C_8H_{12}N_4O_2$	170–171	65	48.97	6.17	28.56	48.82	6.18	28.46
3-Phenyl-6-pyridazonyl-1-acetic	$C_{12}H_{12}N_4O_2$	211–213	75	59.01	4.95	22.94	59.12	5.06	22.94
3-(*p*-Bromophenyl)-6-pyridazonyl 1-acetic[d]	$C_{12}H_{11}BrN_4O_2$	223–226	56	44.60	3.43	17.34	44.76	3.53	17.28

[a] Reaction carried out for 24 hours at 120°. [b] Reaction carried out for 24 hours at 130°. [c] Reaction carried out for 65 hours at 120°. [d] Reaction carried out for 4 hours at 100°.

acetate gave ethyl (3,4-dimethyl-6-pyridazonyl-1)-acetate in 69% yield boiling at 130° (0.2 mm.).

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.02; H, 6.76; N, 13.24.

Ethyl (3,4,5-Trimethyl-6-pyridazonyl-1)-acetate.—To a solution of sodium (4.6 g., 0.2 mole) in 200 ml. of absolute ethanol there was added 3,4,5-trimethyl-6-pyridazone (27.6 g., 0.2 mole). This solution was stirred at less than 10° while ethyl bromoacetate (33.4 g., 0.2 mole) was added dropwise. After the addition was complete the reaction mixture was heated under reflux for one hour. An additional 100 ml. of absolute ethanol was added and the boiling mixture was filtered to remove sodium bromide. The filtrate was chilled giving 24 g. (54% yield) of material melting at 122–126°. A small sample after recrystallization from ethanol melted at 123–126°.

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 59.02; H, 7.31; N, 12.47.

Ethyl (3-Ethyl-6-pyridazonyl-1)-acetate.—By the procedure used to prepare ethyl β-(3-methyl-6-pyridazonyl-1)-propionate, 3-ethyl-6-pyridazone and ethyl bromoacetate gave ethyl (3-ethyl-6-pyridazonyl-1)-acetate in 70% yield boiling at 110–111° (0.09 mm.). This material later crystallized and melted at 48–50°.

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.25; H, 6.65; N, 13.27.

Ethyl (3-Phenyl-6-pyridazonyl-1)-acetate.—By the procedure used to prepare ethyl (3,4,5-trimethyl-6-pyridazonyl-1)-acetate, 3-phenyl-6-pyridazone[15] and ethyl bromoacetate gave ethyl (3-phenyl-6-pyridazonyl-1)-acetate in 66% yield melting at 100–102°.

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.18; H, 5.38; N, 10.80.

Ethyl 3-(*p*-Bromophenyl)-6-pyridazonyl-1-acetate.—By the procedure used to prepare ethyl (3,4,5-trimethyl-6-pyridazonyl-1)-acetate, 3-(*p*-bromophenyl)-6-pyridazone[16] and ethyl bromoacetate gave ethyl 3-(*p*-bromophenyl)-6-pyridazonyl-1-acetate in 53% yield melting at 171–172°.

Anal. Calcd. for $C_{14}H_{13}BrN_2O_3$: C, 49.87; H, 3.89; N, 8.31. Found: C, 49.97; H, 3.87; N, 8.31.

Preparation of Hydrazides.—All of the hydrazides were prepared by heating the corresponding ester with a slight excess of hydrazine hydrate in a solvent, usually ethanol, after which the solvent was removed under vacuum and the residue was crystallized from a suitable solvent, usually benzene or ethanol. Certain of the esters with higher molecular weights or with a greater amount of steric hindrance required higher temperatures for the reaction to proceed. These reactions were carried out in *n*-propyl alcohol. The hydrazides, with pertinent data concerning preparation and properties, are listed in Table I.

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