aside to crystallize. The crystalline cake was broken up, filtered and dried; yield 55.7 g. (89.2%), m.p. 128.0–129.5°. Recrystallized from a mixture of ethyl acetate and ethanol, the salt melted at 131.0–132.5°; yield 49.3 g. (79%).

In like manner there was obtained a 90.7% yield of 2-diethylaminoethyl α-(2-cyclohexen-1-yl)-2-thienylacetate hydrochloride, melting at 151.5–153°. Recrystallization from an ethyl acetate–ethanol mixture yielded a product which melted at 152.0 to 153.5°; yield 80% based on starting materials.

Method I.—A mixture of 14.8 g. (0.127 mole) of 2-diethylaminoethanol, 25.0 g. (0.106 mole) of ethyl α-(2-cyclopenten-1-yl)-2-thienylacetate, 0.28 g. (0.012 mole) of sodium and 170 ml. of dry xylene in a 500-ml. flask equipped with a short fractionating column was slowly distilled during a period of six hours. A mixture of alcohol and xylene was collected first and then xylene (total volume of distillate 68 ml.). The cooled reaction mixture was washed neutral and concentrated *in vacuo* to a brown oil which distilled at 115–123° (0.001 mm.), $n^{20}D$ 1.5170; yield 20.1 g. The distillate was dissolved in 80 ml. of ethyl acetate and treated with 14.6 ml. of 4.47 *N* ethanolic hydrochloric acid. The salt, 2-diethylaminoethyl α-(2-cyclopenten-1-yl)-2-thienylacetate hydrochloride was obtained in 42% yield (15 g.) and melted at 131–132.5° before crystallization, 134–135° after recrystallization from a mixture of ethyl acetate and ethanol.

From 25 g. (0.106 mole) of methyl α-(2-cyclohexen-1-yl)-2-thienylacetate and the same quantities of reagents used in the preparation of the 2-cyclopenten-1-yl ester described above, there was obtained 27.1 g. of 2-diethylaminoethyl α-(2-cyclohexen-1-yl)-2-thienylacetate, b.p. 135–145° (0.001 mm.), $n^{20}D$ 1.5222, which was converted to its hydrochloride with alcoholic hydrochloric acid; yield 26.5 g. (70%), m.p. 151–154°.

Acknowledgment.—Mr. Ralph Pulliam provided valuable technical assistance. Mr. Jerome Genzer coöperated in the study of the alkylation of 2-thienylacetonitrile. Microanalyses were carried out by Dr. Fritz Buhler in the Microanalytical Laboratory of this Institute.

NEW YORK 11, NEW YORK

[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

The Preparation of Some Pyridazonyl Acids

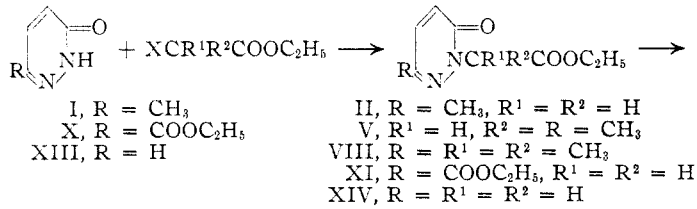
BY JOHN A. KING AND FREEMAN H. MCMILLAN

RECEIVED NOVEMBER 26, 1951

6-Methyl-3-pyridazone has been alkylated in the 2-position with α-halo esters of acetic, propionic and isobutyric acids and both 6-carbethoxy-3-pyridazone and 3-pyridazone have been similarly alkylated with haloacetic esters. All of the esters were hydrolyzed to the corresponding acids and three of these acids were converted to methyl ketone.

As a part of some exploratory work in the field of pyridazine chemistry we considered it desirable to study a series of 2-(3-pyridazonyl)-acetic acids and their derivatives, a description of the preparation of which forms the subject of the present paper.

6-Methyl-3-pyridazone (I) underwent ready alkylation on the nitrogen with ethyl bromoacetate in the presence of sodium ethoxide; the resultant ester (II) was hydrolyzed to the acid III, as well as ammonolyzed to the corresponding amide of III.



I, R = CH_3
X, R = $COOC_2H_5$
XIII, R = H

II, R = CH_3, R^1 = R^2 = H
V, R^1 = H, R^2 = R = CH_3
VIII, R = R^1 = R^2 = CH_3
XI, R = $COOC_2H_5$, R^1 = R^2 = H
XIV, R = R^1 = R^2 = H

III, R = CH_3, R^1 = R^2 = H
VI, R^1 = H, R = R^2 = CH_3
IX, R = R^1 = R^2 = CH_3
XII, R = COOH, R^1 = R^2 = H
XV, R = R^1 = R^2 = H

IV, R = CH_3, R^1 = R^2 = H
VII, R^1 = H, R = R^2 = CH_3
XVI, R = R^1 = R^2 = H

The diethyl amide of III was prepared by the alkylation of I with N,N-diethylchloroacetamide, while the anilide of III was prepared from III directly. As proof that alkylation of I had occurred on nitrogen instead of on oxygen the acid III was thermally decarboxylated to 2,6-dimethyl-3-pyridazone, identical with a sample prepared by methylation of I by the procedure of Homer[1] and co workers, who proved the structure of their material The acid III, on treatment with acetic anhydride and pyridine gave a good yield of the acetone derivative IV.

Substitution of ethyl α-bromopropionate for ethyl α-bromoacetate in the alkylation of I furnished the corresponding propionic ester V; this was hydrolyzed to the acid VI which was converted, by acetic anhydride and pyridine, to the methyl ethyl ketone derivative VII. Similarly, ethyl α-bromoisobutyrate alkylated I to produce the tri-substituted acetic acid ester VIII. The ester group of VIII could be removed by hydrolysis to the acid IX, but the latter substance could not be converted to a ketone by acetic anhydride and pyridine, the acid being recovered unchanged.

The methyl group in I was oxidized to a carboxyl which was esterified to give X, by procedures essentially as described[2] in the literature. N-Methylation of X was easily accomplished and the resultant ester was hydrolyzed to 6-(2-methyl-3-pyridazonyl)-carboxylic acid. Alkylation of X with ethyl bromoacetate afforded the ester XI, which was hydrolyzed to the corresponding acid XIII.

Decarboxylation of the acid I, R = COOH, produced 3-pyridazone (XIII) which was similarly condensed with ethyl chloroacetate, giving the ester

(1) R. F. Homer, H. Gregory and L. F. Wiggins, *J. Chem. Soc.*, 2191 (1948).

(2) R. F. Homer, H. Gregory, W. G. Overend and L. F. Wiggins, *ibid.*, 2195 (1948).

XIV. This ester was hydrolyzed to the acid XV, and the latter substance, on treatment with acetic anhydride and pyridine, gave rise to the acetone derivative XVI.

Experimental Part[3,4]

Ethyl 2-(6-Methyl-3-pyridazonyl)-acetate (II).—Sodium (23 g., 1.00 mole) was dissolved in absolute ethanol (450 cc.) contained in a 2-liter 3-necked flask fitted with a stirrer, dropping funnel, immersed thermometer and reflux condenser. The stirred sodium ethoxide solution was cooled to 10° and there was added 6-methyl-3-pyridazone (I)[5] (110 g., 1.00 mole) followed by the dropwise addition, while the reaction temperature was maintained at 15–20°, of ethyl bromoacetate (167 g., 1.00 mole). After the addition was complete the mixture was refluxed one hour, cooled and filtered. The alcohol was removed from the filtrate under vacuum and the residue was taken up in benzene (500 cc.). A small additional amount of sodium bromide was removed by filtration and the benzene solution was then fractionally distilled to give 160 g. (82% yield) of product, b.p. 159–167° (5–6 mm.), which crystallized in the receiver. After recrystallization from benzene it melted at 77.5–79°.

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.10; H, 6.17; N, 14.28. Found: C, 55.35; H, 5.85; N, 14.41.

2-(6-Methyl-3-pyridazonyl)-acetic Acid (III).—A mixture of ethyl 2-(6-methyl-3-pyridazonyl)-acetate (40 g., 0.2 mole) and 5% hydrochloric acid (200 cc.) was refluxed two hours, during which time the crystalline acid started separating. The mixture was chilled and filtered to give 30.6 g. (91% yield) of product, m.p. 237–240° (dec.).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.79; N, 16.66. Found: C, 50.05; H, 5.05; N, 16.45.

Two hours refluxing with five times its weight of 10% sodium hydroxide solution, followed by acidification, gave an equally good yield of acid from the ester.

2-(6-Methyl-3-pyridazonyl)-acetamide.—Sixteen grams (0.08 mole) of ethyl 2-(6-methyl-3-pyridazonyl)-acetate was added to concentrated (28%) aqueous ammonia (160 cc.) with swirling and the resultant solution was chilled in an ice-bath for 30 minutes. The crystalline amide was removed by filtration and recrystallized from 80 cc. of water to give 9.5 g. (71% yield) of product, m.p. 224–225°.

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.35; H, 5.42; N, 25.15. Found: C, 50.25; H, 5.19; N, 25.13.

N,N-Diethyl 2-(6-Methyl-3-pyridazonyl)-acetamide.—6-Methyl-3-pyridazone (22.0 g., 0.2 mole) was added to a stirred solution of sodium (4.6 g., 0.2 mole) in ethanol (100 cc.), followed by the dropwise addition of N,N-diethyl chloroacetamide[6] (30.0 g., 0.2 mole). The reaction mixture became turbid and its temperature gradually rose to 47° during the addition. The mixture was then refluxed for 15 hours and filtered hot. The filtrate was evaporated to dryness under vacuum and the residue was recrystallized from alcohol–ether to give 4.9 g. (11% yield) of product, m.p. 110.5–112°. The filtrate from this crystalline material was fractionally distilled to give an additional 19.5 g. (44% yield; total, 24.4 g., 55% yield) of product, b.p. 160–164° (0.15 mm.) which crystallized in the distillation apparatus. The recrystallized material was analyzed.

Anal. Calcd. for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.67; N, 18.82. Found: C, 59.05; H, 7.39; N, 18.68.

2-(6-Methyl-3-pyridazonyl)-acetanilide.—Ten grams (0.06 mole) of 2-(6-methyl-3-pyridazonyl)-acetic acid and 20 g. (0.22 mole) of aniline were heated to reflux (*ca.* 200°) under an air condenser for 2.5 hours. The resultant mixture, which crystallized on cooling, was recrystallized from alcohol (400 cc.) to give 12.4 g. (85% yield) of the anilide, m.p. 203–204°.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.29. Found: C, 64.25; H, 5.57; N, 17.39.

Decarboxylation of 2-(6-Methyl-3-pyridazonyl)-acetic Acid. 2,6-Dimethyl-3-pyridazone.—1.68 grams (0.01 mole) of 2-(6-methyl-3-pyridazonyl)-acetic acid was placed in a 10-cc. round-bottomed flask and heated in an oil-bath at 245–250° until gas evolution ceased. The residue was distilled at atmospheric pressure, b.p. 234–236°, the distillate crystallizing almost immediately. The distillate weighed 0.95 g. (77% yield), melted at 44–47°, and was identical with a sample of the material, m.p. 47–48.5°, prepared from 6-methyl-3-pyridazone and methyl iodide in the presence of sodium ethoxide by the procedure of Homer and co-workers.[1]

2-(6-Methyl-3-pyridazonyl)-acetone (IV).—A mixture of 2-(6-methyl-3-pyridazonyl)-acetic acid (16.8 g., 0.10 mole) acetic anhydride (50 cc.) and pyridine (34 cc.) was refluxed for two hours, during which time there was copious evolution of carbon dioxide. The excess reagents were removed under vacuum to leave a gummy residue which soon solidified and was recrystallized from ethanol-Skellysolve B and from benzene. There was obtained a total of 9.6 g. (62% yield) of product which melted, after another recrystallization, at 99.5–100°

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.81; H, 6.07; N, 16.86. Found: C, 57.60; H, 6.22; N, 16.71.

The semicarbazone, prepared in the usual manner, melted at 204–205° (dec.) after suitable recrystallization from alcohol.

Anal. Calcd. for $C_9H_{13}N_5O_2$: C, 48.43; H, 5.87. Found: C, 47.85; H, 5.61.

Ethyl α-[2-(6-Methyl-3-pyridazonyl)]-propionate (V).—To a stirred solution of sodium (6.9 g., 0.3 mole) in ethanol (150 cc.) there was added 6-methyl-3-pyridazone (33 g., 0.3 mole) and then while the temperature of the stirred reaction mixture was held at 15–20° there was added, during ten minutes, ethyl α-bromopropionate (54.3 g., 0.3 mole). The mixture was then refluxed with stirring for 45 minutes, cooled, filtered and the filtrate taken to dryness under vacuum. The residue was partitioned between benzene (200 cc.) and water (100 cc.) and the benzene layer was fractionally distilled to give 41.4 g. (66% yield) of product, b.p. 97–101° (0.1–0.2 mm.), $n^{25}D$ 1.5025, sp. gr.$^{25}_{25}$ 1.1423.

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.14; H, 6.71; N, 13.33. Found: C, 57.25; H, 6.78; N, 13.17.

α-[2-(6-Methyl-3-pyridazonyl)]-propionic Acid (VI).—Twenty-seven grams (0.129 mole) of the corresponding ethyl ester was refluxed for one hour with 130 cc. of 10% sodium hydroxide. The solution was acidified (hydrochloric acid), concentrated to incipient crystallization, and then chilled. Filtration furnished 23.1 g. (99% yield) of product, m.p. 141–142° after recrystallization from water.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.73; H, 5.53; N, 15.38. Found: C, 52.45; H, 5.49; N, 14.91.

Methyl 1-[2-(6-Methyl-3-pyridazonyl)]-ethyl Ketone (VII).—A mixture of α-2-(6-methyl-3-pyridazonyl)-propionic acid (12.0 g., 0.068 mole), acetic anhydride (60 cc.) and pyridine (40 cc.) was refluxed two hours, during which time carbon dioxide was freely evolved. The reaction mixture was fractionally distilled to give 9.4 g. (78% yield) of product, b.p. 94–99° (0.4 mm.), $n^{25}D$ 1.5226.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.52; H, 6.55; N, 15.65.

The semicarbazone of the ketone, prepared in the usual manner, melted at 201–202° after suitable recrystallization from water.

Anal. Calcd. for $C_{10}H_{15}N_5O_2$: N, 29.55. Found: N, 29.23.

Ethyl α-Methyl-α-[2-(6-methyl-3-pyridazonyl)]-propionate (VIII).—6-Methyl-3-pyridazone (44.0 g., 0.40 mole) was added to a solution of sodium (10.0 g., 0.44 mole) in ethanol (400 cc.), followed by the addition of ethyl α-bromoisobutyrate (86.0 g., 0.44 mole). The mixture was refluxed with stirring for four hours, then cooled, diluted with three volumes of ether and filtered through Supercel. The filtrate was taken to dryness under vacuum and the residue boiled with benzene; after filtration the benzene solution was fractionally distilled to give 16.5 g. (18% yield) of product, b.p. 105–114° (0.3 mm.).

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.89; H, 7.19; N, 12.49. Found: C, 59.12; H, 7.45; N, 12.38.

α-Methyl-α-[2-(6-methyl-3-pyridazonyl)]-propionic Acid (IX).—The corresponding ethyl ester was hydrolyzed, in 36% yield, to the acid by 3 hours refluxing with 10% hydro-

(3) All melting points and boiling points are uncorrected.

(4) Microanalyses were carried out in these laboratories, under the direction of Dr. F. A. Buehler.

(5) W. G. Overend and L. F. Wiggins, *J. Chem. Soc.*, 239 (1947).

(6) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 149 (1915).

chloric acid. The acid, after recrystallization from alcohol, melted at 214–214.5°.

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 54.84; H, 6.18; N, 13.92.

When 2.0 g. of this acid was refluxed for 3 hours with acetic anhydride (11 g.) and pyridine (7.5 g.) no evolution of carbon dioxide occurred, and working up of the reaction mixture gave only unchanged starting material, m.p. 212–214°.

Ethyl 6-(2-Methyl-3-pyridazonyl)-carboxylate.—6-Methyl-3-pyridazone (I) was oxidized to 6-(3-pyridazonyl)-carboxylic acid, m.p. 257° (dec.), in 76% yield by the potassium dichromate–sulfuric acid method described by Homer and co-workers[2]; this acid was converted to its ethyl ester, X, m.p. 127–128° (reported[2] m.p. 122°) essentially as described by the same authors and was ammonolyzed to the amide, m.p. 314–315° (dec.) (reported[2] m.p. 304°) more conveniently at room temperature in aqueous solution than in the described alcoholic solution at 0°; it was also aminolyzed to the anilide by heating a mixture of 1.7 g. (0.01 mole) of the ester and 0.93 g. (0.01 mole) of aniline at 180° for 30 minutes and then at 195° for one hour, after which the mixture crystallized on cooling and after two recrystallizations from ethanol melted at 254.5–256°.

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.21; N, 19.53. Found: C, 61.15; H, 4.00; N, 19.66.

To a solution of ethyl 6-(3-pyridazonyl)-carboxylate (X) (16.8 g., 0.10 mole) and methyl iodide (21.3 g., 0.15 mole) in absolute alcohol (100 cc.) there was added dropwise a solution of sodium (2.5 g., 0.11 mole) in absolute alcohol (100 cc.) while the temperature of the stirred reaction mixture was maintained at 25°. After the addition was complete the reaction mixture was refluxed 30 minutes, cooled and filtered. The filtrate was taken to dryness under vacuum, the residue was taken up in benzene (150 cc.) and additional sodium iodide was removed by filtration. After removal of the benzene the residue was crystallized from Skellysolve B plus a few drops of benzene to give a total of 12 g. (66% yield) of product which, after another recrystallization, melted at 67.5–68°.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.75; H, 5.54; N, 15.38. Found: C, 52.70; H, 5.46; N, 15.41.

6-(2-Methyl-3-pyridazonyl)-carboxylic Acid.—This was prepared by 1:1 hydrochloric acid hydrolysis, for one hour, of a small amount of its ethyl ester. After recrystallization from water it melted at 237–238° (dec.).

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.75; H, 3.93; N, 18.18. Found: C, 46.70; H, 4.07; N, 18.30.

Ethyl 2-(6-Carbethoxy-3-pyridazonyl)-acetate (XI).—To a stirred mixture of ethyl 6-(3-pyridazonyl)-carboxylate (8.4 g., 0.05 mole) and ethyl bromoacetate (8.4 g., 0.05 mole) in ethanol (100 cc.) there was added during 15 minutes, while the temperature of the reaction mixture was maintained at 15–20°, an alcoholic solution of sodium ethoxide (prepared from 1.2 g. of sodium in 50 cc. of absolute alcohol). The resultant white precipitate dissolved when the mixture was heated to reflux, at which temperature it was held for one hour. The mixture was then cooled and filtered and the filtrate was taken to dryness under vacuum to leave a white residue which after recrystallization from aqueous alcohol weighed 7.8 g. (61% yield) and melted at 82–83°.

Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 52.05; H, 5.40; N, 10.96.

2-(6-Carboxy-3-pyridazonyl)-acetic Acid (XII).—The diester XI (3.4 g., 0.013 mole) was refluxed 20 hours with 25 cc. of 1:1 hydrochloric acid and the solution was then taken to dryness under vacuum. Recrystallization of the residue from water gave 1.4 g. of product, m.p. 220–223°.

Anal. Calcd. for $C_7H_6N_2O_5$: C, 42.43; H, 3.05; N, 14.14. Found; C, 42.20; H, 3.18; N, 14.02.

Ethyl 2-(3-Pyridazonyl)-acetate (XIV).—To a solution of 3-pyridazone (XIII) (m.p. 100–103°, prepared in 82% yield by thermal decarboxylation at 275° of 6-carboxy-3-pyridazone as described by Homer and co-workers[2]) (27.4 g., 0.29 mole) in alcoholic sodium ethoxide (prepared by dissolving 6.6 g. of metallic sodium in 285 cc. of absolute alcohol) there was added dropwise the ethyl chloroacetate (35 g., 0.29 mole) while the reaction mixture was refluxed one hour and then filtered. The filtrate was taken to dryness under vacuum and the residue was distilled to give 33.4 g. (64% yield) of product, b.p. 109–117° (0.35–0.9 mm.), which crystallized in the receiver. After recrystallization from Skellysolve B plus a little benzene the material melted at 52.5–53°.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.75; H, 5.54; N, 15.38. Found: C, 52.85; H, 5.61; N, 14.86.

2-(3-Pyridazonyl)-acetic Acid (XV).—This was prepared, in 66% yield, by one hour hydrolysis with 1:1 hydrochloric acid of the corresponding ethyl ester. After recrystallization from water the acid melted at 174–175°.

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.75; H, 3.92; N, 18.18. Found: C, 46.63; H, 3.72; N, 18.08.

2-(3-Pyridazonyl)-acetone (XVI).—A mixture of 2-(3-pyridazonyl)-acetic acid (15.3 g., 0.10 mole), acetic anhydride (100 cc.) and pyridine (100 cc.) was refluxed two hours and then taken to dryness under vacuum. The residue was partitioned between benzene and 10% aqueous potassium carbonate solution, the benzene layer was separated and evaporated to leave 3.4 g. (22% yield) of ketone which after sublimation at 0.15 mm. (bath at 100°) followed by recrystallization from Skellysolve B–benzene melted at 98–99°.

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.42. Found: C, 55.24; H, 5.05; N, 18.69.

A quarter of a gram of the ketone was converted to its semicarbazone in the usual manner. This derivative, after recrystallization from water, melted at 215–216°.

Anal. Calcd. for $C_8H_{11}N_5O_2$: N, 33.48. Found: N, 33.20.

We wish to acknowledge the technical assistance of Messrs. Charles Anderson and Kenneth Hutton.

NEW YORK 11, N. Y.