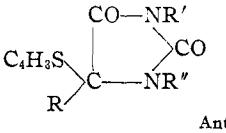
TABLE V

N-ALKYL-5-SUBSTITUTED-5-(2-THIENYL)-HYDANTOINS



R	R′	R″	Yield, %	M.p., °C.	Nitrogen, % Calcd.	Found	Anti-convulsant activity[a]
C_2H_5	CH_3	H	70	140.8–141.1	12.49	12.36	0
C_2H_5	C_2H_5	H	47	109.5–110	11.76	12.04	0
n-C_4H_9	CH_3	H	100	145–146	11.11	11.02	0
n-C_4H_9	C_2H_5	H	70	90.5–91	10.52	10.27	0
C_6H_{11}	CH_3	H	95	198–199	10.07	10.03	25
C_6H_5	CH_3	H	80	155–155.5	10.28	10.13	0
C_6H_5	C_2H_5	H	75	116–117	9.79	9.72	0
C_6H_5	CH_3	CH_3	12	139–140	9.79	9.76	50
2-C_4H_3S	CH_3	H	78	165–166.5	10.07	10.10	0

[a] Per cent. of activity of dillantin. Equal doses of 50 mg./kg. by mouth in cats using electroshock test.

obtained in this fashion weighs 3.4 g. and consists of impure 5-ethyl-5-(2-thienyl)-hydantoin. The ether solution is evaporated giving 3.6 g. of crude product, a yield of 47%. After two recrystallizations from dilute alcohol the compound melts at 109.5–110°

The 3-alkyl-5-substituted-5-(2-thienyl)-hydantoins are soluble in 5% NaOH solution. 1,3-Dimethyl-5-phenyl-5-(2-thienyl)-hydantoin is obtained as a co-product from the preparation of 3-methyl-5-phenyl-5-(2-thienyl)-hydantoin by extracting the ether solution of the crude reaction product with 5% Na_2CO_3 solution and 5% NaOH solution successively. The Na_2CO_3 solution contains a trace of unreacted 5-phenyl-5-(2-thienyl)-hydantoin; the NaOH solution contains 3-methyl-5-phenyl-5-(2-thienyl)-hydantoin; and from the ether solution by evaporation there is obtained a small amount (12%) of 1,3-dimethyl-5-phenyl-5-(2-thienyl)-hydantoin. The melting points, yields and other data for the 3-alkyl-5-substituted-5-(2-thienyl)-hydantoins are shown in Table V.

DENTON, TEXAS

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Pyridazine Derivatives. I. Some Amebacidal 3-Pyridazones

BY EDGAR A. STECK, R. PAULINE BRUNDAGE AND LYNN T. FLETCHER

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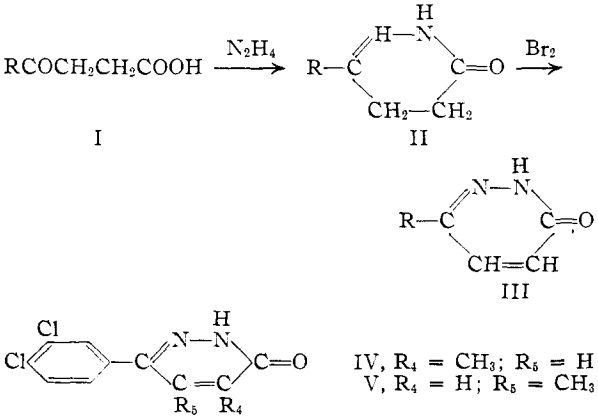
The investigation of a series of 6-substituted 4,5-dihydro-3-pyridazones and related 3-pyridazones led to the preparation of 6-(3,4-dichlorophenyl)-3-pyridazone, a new type compound to show amebacidal activity (hamster test).

Pyridazine derivatives do not appear to occur in natural products, and also have been relatively neglected in the investigation of potential pharmaceuticals. Some pyridazines have been examined for activity against sporozoan (SN[1] 416, 497, 498, 5388, 10959, 11065 and 11066) and flagellate[2] parasites, but not for antiamebic activity. The present phase of our work has centered about the preparation of 6-(4-halophenyl)-3-pyridazones for study as amebacides; details concerning the testing of the compounds will be reported elsewhere.

The requisite 6-substituted 3-pyridazones were made by action of hydrazine upon 1,4-dicarbonyl compounds, much after the method first found to yield a pyridazine type.[3] Application of the scheme to 4-substituted-4-oxobutanoic acids (I) to obtain 6-substituted 4,5-dihydro-3-pyridazones (II) and the dehydrogenation of II to the corresponding 3-pyridazones (III) has been well described (*e.g.*, refs. 4–8). The present investigation has led to the synthesis of the 3-pyridazones bearing in position 6 the following groups: 4-chlorophenyl-, 4-bromophenyl-, 5-iodophenyl-, 4-(2,4-dichlorophenyl)- and 4-(3,4-dichlorophenyl)-. There was also prepared from appropriate oxobutanoic acids, the compounds (IV) and (V) as examples of 4/5-alkyl-6-(3,4-dichlorophenyl)-3-pyridazones. When screened for amebacidal activity in the hamster (*Cricetus auratus*),[9] the most effective of the highly insoluble 3-pyridazones was 6-(3,4-dichlorophenyl)-3-pyridazone. It appears that this type of intestinal amebacide may exert its action by achieving useful concentration in the intestinal lumen through low solubility and/or retarded absorption (*cf.* refs. 10a, 10b).



I II III

IV, $R_4 = CH_3$; $R_5 = H$
V, $R_4 = H$; $R_5 = CH_3$

In the present work, the ketonic acids of structure (I) were made by interaction of aromatic types with succinic anhydride under Friedel–Crafts conditions.[11] The greater number of these intermediates were known (the 4-(4-chlorophenyl)-, 4-(4-bromophenyl)- and 4-(4-iodophenyl)-4-oxo-

(1) All compounds designated SN (Survey Number) have been tabulated, together with antimalarial activities, in the monograph, "Antimalarial Drugs, 1941–1945" (F. Y. Wiselogle, editor), Edwards Bros., Ann Arbor, Mich., 1946.

(2) E. Walton, British Patent 573,770.

(3) L. Knorr, *Ber.*, **18**, 305 (1885).

(4) T. Curtius, *J. prakt. Chem.*, [2] **50**, 522 (1894).

(5) R. von Rothenburg, *ibid.*, [2] **51**, 141 (1895).

(6) R. Fittig, *Ann.*, **299**, 16 (1898).

(7) S. Gabriel and J. Colman, *Ber.*, **32**, 395 (1899).

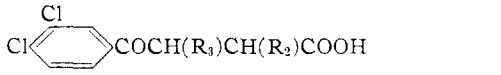
(8) O. Poppenberg, *ibid.*, **34**, 3257 (1901).

(9) E. W. Dennis, D. A. Berberian and S. Hansen, *Am. J. Trop. Med.*, **29**, 683 (1949).

(10) (a) N. J. Conan, Jr., J. A. Head and A. E. Brewer, *Trans. Roy. Soc. Trop. Med. Hyg.*, **43**, 659 (1950); (b) N. J. Conan, Jr., *Am. J. Trop. Med.*, **31**, 18 (1951).

(11) E. Berliner, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., p. 229.

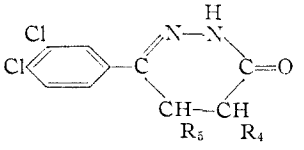
butanoic acids had been made previously; 4-(2,4-dichlorophenyl)- and 4-(3,4-dichlorophenyl)-4-oxobutanoic acids were new). Methylsuccinic anhydride was caused to react with 1,2-dichlorobenzene in the usual manner and a mixture of 4-(3,4-dichlorophenyl)-2-methyl-4-oxobutanoic acid (VI) and the 3-methyl congener (VII) was obtained. Structures were assigned to the isomers on the basis of physical properties, as indicated from related data on the 4-phenyl types.[12-14] Total purification of the fraction which was chiefly 4-(3,4-dichlorophenyl)-3-methyl-4-oxobutanoic acid (VII) was unduly wasteful and laborious; the separation of the two series was accomplished most effectively at the 3-pyridazone stage. 1,2-Dibromobenzene gave a mixture of substances, including



VI, $R_2 = CH_3$; $R_3 = H$
VII, $R_2 = H$; $R_3 = CH_3$

1,4-dibromobenzene and 4-(4-bromophenyl)-4-oxobutanoic acid, but no dibromo acid. 1,4-Dichlorobenzene produced only tarry material in numerous attempts to effect reaction with succinic anhydride, and trials with 1,2,4-trichlorobenzene and 1,2,4,5-tetrachlorobenzene were likewise unsuccessful.

The 6-substituted 4,5-dihydro-3-pyridazones (structure II) were obtained by action of hydrazine upon the appropriate 4-aryl-4-oxobutanoic acid (I).[4,5,7,8] In the case of the reaction of 4-(3,4-dichlorophenyl)-2/3-methyl-4-oxobutanoic acids [(VI) and (VII)] with hydrazine there were produced 6-(3,4-dichlorophenyl)-4,5-dihydro-4-methyl-3-pyridazone (VIII) and an impure sample of the related 5-methyl isomer (IX). The latter was freed of contaminants (chiefly VIII) at the pyridazone stage.



VIII, $R_4 = CH_3$; $R_5 = H$
IX, $R_4 = H$; $R_5 = CH_3$

Dehydrogenation of the 6-aryl 4,5-dihydro-3-pyridazones (II) to the corresponding 3-pyridazones (III) was accomplished by bromine in glacial acetic acid (*cf.* refs. 4–8). It was at this step that the 4/5-methyl types IV and V were obtained in pure form. The isolation of pure 6-(3,4-dichlorophenyl)-4,5-dihydro-5-methyl-3-pyridazone (IX) was not readily possible, but oxidation of the contaminated material produced a mixture which could be separated by crystallization. 6-(3,4-Dichlorophenyl)-5-methyl-3-pyridazone (V) and the isomer IV were separated in a ratio of two to one. The latter compound was also obtained (*cf.* ref. 14) by the action of bromine on VIII.

(12) F. Mayer and G. Stamm, *Ber.*, **56**, 1424 (1923).
(13) F. Krollpfeiffer and W. Schäffer, *ibid.*, **56**, 630 (1923).
(14) A. Oppenheim, *ibid.*, **34**, 4227 (1901).

Experimental[15]

A. 4-Substituted 4-Oxobutanoic Acids.—4-(4-Chlorophenyl)-4-oxobutanoic acid[16,17] and the related bromo[18] and iodo[19] compounds were prepared as described in the literature.

I. 4-(2,3- and 3,4-Dichlorophenyl)-4-oxobutanoic Acids.—The reactions of 1,2- and 1,3-dichlorobenzene with succinic anhydride and aluminum chloride were run in an excess of the dichlorobenzene at *ca.* 65–70° in the usual manner (*cf.* ref. 11). Structures of the products were proven by oxidation to the dichlorobenzoic acids.

4-(3,4-Dichlorophenyl)-4-oxobutanoic acid was obtained in 58% yield[20] in the form of white prismatic needles from ethanol or benzene; m.p. 166–166.7°.

Anal. Calcd. for $C_{10}H_8Cl_2O_3$: C, 48.61; H, 3.26; Cl, 28.70. Found: C, 48.54; H, 3.08; Cl, 28.45.

The related 4-(2,4-dichlorophenyl) compound separated from heptane as white prisms, m.p. 77.5–78°, yield 13%.[20]

Anal. Found: C, 48.77; H, 3.39; Cl, 28.36.

II. 6-(3,4-Dichlorophenyl)-2/3-methyl-4-oxobutanoic Acids (VI and VII).—The preparation of VI and VII was accomplished by using methylsuccinic anhydride[21,22] in a Friedel–Crafts reaction with 1,2-dichlorobenzene. A vigorously stirred mixture of 11.4 g. (0.1 mole) methylsuccinic anhydride and 40 cc. of tech. 95% 1,2-dichlorobenzene was treated with 27.0 g. (0.2 mole) powdered anhydrous aluminum chloride. The temperature rose to 65–70° during the addition and was then heated at *ca.* 65° for one hour before quenching and working up the products (*cf.* ref. 23). A 70% yield of crude mixture of 4-(3,4-dichlorophenyl)-2/3-methyl-4-oxobutanoic acid resulted. Repeated crystallization from heptane and from benzene afforded a 17% yield of pure 4-(3,4-dichlorophenyl)-2-methyl-4-oxobutanoic acid (A), m.p. 123.5–124°. Complete purification of the more soluble 3-methyl isomer was almost impossible, and a 12% yield of impure compound (B) of m.p. 100–108° was obtained. The material (B) was employed as such in the remainder of the synthesis, and the separation of isomers could be accomplished most satisfactorily at the 3-pyridazone stage (see B, II and C, II).

Anal. Calcd. for $C_{11}H_{10}Cl_2O_3$: C, 50.60; H, 3.86; neut. equiv., 261.1. Found: (A) C, 50.79; H, 4.10; neut. equiv., 262.2; (B) neut. equiv., 252.

B. 6-Substituted 4,5-Dihydro-3-pyridazones.—The general scheme employed for conversion of the 4-substituted 4-oxobutanoic acids (I) into 6-substituted 4,5-dihydro-3-pyridazones (II) was essentially that of Curtius,[4] with the procedure similar to that followed by Gabriel and Colman.[7] A solution of the acid in one equivalent of *N* potassium hydroxide was warmed to 80–90° and a solution of a 10–15% excess of hydrazine sulfate in one equivalent of *N* potassium hydroxide, also at 80–90°, was added. The mixture was heated under reflux, on the steam-bath, for one to two hours. In most cases, the 6-substituted 4,5-dihydro-3-pyridazones separated during the heating.

I. 6-(4-Halophenyl)-4,5-dihydro-3-pyridazones.—6-(4-Chlorophenyl)-4,5-dihydro-3-pyridazone was isolated in 88% yield; white prisms from ethanol, m.p. 179–179.5° (lit.[16] m.p. 178°).

(15) All melting points are corrected for thermometer stem exposure.
(16) S. Skraup and E. Schwamberger, *Ann.*, **462**, 135 (1938).
(17) C. F. H. Allen, J. B. Normington and C. V. Wilson, *Can. J. Research*, **11B**, 382 (1934).
(18) L. F. Fieser and A. M. Seligman, THIS JOURNAL, **60**, 173 (1938).
(19) L. F. Fieser, E. Berliner, F. J. Bonthius, F. C. Chang, W. G. Dauben, M. G. Ettlinger, G. Fawaz, M. Fields, C. Heidelberger, H. Heymann, W. R. Vaughan, A. G. Wilson, E. Wilson, M.-I. Wu, M. T. Leffler, K. E. Hamlin, E. J. Matson, E. E. Moore, M. B. Moore and H. E. Zaugg, *ibid.*, **70**, 3002 (1948).
(20) Compare with yield of related aroylacrylic acid: D. Papa, E. Schwenk, F. Villani and E. Klingsberg, *ibid.*, **70**, 3356 (1948).
(21) R. Kitchen and R. B. Sandin, *ibid.*, **67**, 1645 (1945).
(22) The authors wish to express their appreciation to Mr. T. M. Melton, formerly of these laboratories, who supplied sodium methylsuccinate after preparing it by catalytic reduction of sodium itaconate with Raney nickel.
(23) E. L. Martin and L. F. Fieser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 182.

Anal. Calcd. for $C_{10}H_9ClN_2O$: Cl, 17.04; N, 13.43. Found: Cl, 17.00; N, 13.62.

6-(4-Bromophenyl)-4,5-dihydro-3-pyridazone, white needles from aqueous ethanol, m.p. 168–168.5°, was obtained in 96% yield.

Anal. Calcd. for $C_{10}H_9BrN_2O$: C, 47.45; H, 3.58; N, 11.07. Found: C, 47.52; H, 3.30; N, 11.22.

4,5-Dihydro-6-(4-iodophenyl)-3-pyridazone was produced in 87% yield; it separated from aqueous ethanol or ethyl acetate as white prismatic needles, m.p. 199–199.5°.

Anal. Calcd. for $C_{10}H_9IN_2O$: C, 40.02; H, 3.02; I, 42.29; N, 9.34. Found: C, 40.07; H, 3.30; I, 42.40; N, 9.53.

6-(2,4-Dichlorophenyl)-4,5-dihydro-3-pyridazone was obtained in 97% yield; it crystallized as white needles from aqueous ethanol, m.p. 172.5–173°.

Anal. Calcd. for $C_{10}H_8Cl_2N_2O$: C, 49.41; H, 3.32; N, 11.32. Found: C, 49.66; H, 3.14; N, 11.40.

6-(3,4-Dichlorophenyl)-4,5-dihydro-3-pyridazone, which separated from ethanol in the form of white blades of m.p. 174–175°, was formed in 96% yield.

Anal. Calcd. for $C_{10}H_8Cl_2N_2O$: C, 49.41; H, 3.32; Cl, 29.17. Found: C, 49.35; H, 3.05; Cl, 29.25, 29.32.

II. **6-(3,4-Dichlorophenyl)-4,5-dihydro-4/5-methyl-3-pyridazones (VIII) and (IX).**—The reaction of 4-(3,4-dichlorophenyl)-2-methyl-4-oxobutanoic acid ((VI), m.p. 123–124°) with hydrazine followed the usual procedure. Pure 6-(3,4-dichlorophenyl)-4,5-dihydro-4-methyl-3-pyridazone (VIII) was obtained in 90% yield; white blades from benzene, m.p. 167–168°.

Anal. Calcd. for $C_{11}H_{10}Cl_2N_2O$: C, 51.38; H, 3.92; N, 10.91. Found: C, 51.16; H, 3.86; N, 10.69.

A mixture of isomers resulted in 85% yield from the interaction of 4-(3,4-dichlorophenyl)-2/3-methyl-4-oxobutanoic acid (m.p. 100–108°) with hydrazine. Although some pure 6-(3,4-dichlorophenyl)-4,5-dihydro-4-methyl-3-pyridazone (m.p. 167–168°) could be isolated by crystallization from benzene, the bulk of material melted below 150° and was used directly in the conversion to 3-pyridazone type (*v.i.*, C, II).

C. **6-Substituted 3-Pyridazones.**—The conversion of 4,5-dihydropyridazones (II) to 3-pyridazones (III) by the action of bromine in acetic acid is a well known method (*cf.* refs. 7, 8). A concentrated solution of the type II in glacial acetic acid was stirred vigorously at 60–70° while 1.1 equivalents of bromine was added. At the end of the addition, the mixture was heated for 1–3 hours to complete the reaction. The hydrobromide was collected after chilling, then washed with cold ethyl acetate before conversion to the base by slurrying with ammonium hydroxide. The bases were washed well with ice-water, then dried.

I. **6-(4-Halophenyl)-3-pyridazones.**—6-(4-Chlorophenyl)-3-pyridazone was produced in 90% yield; it separated from butanol as white needles, m.p. 270–270.5°

Anal. Calcd. for $C_{10}H_7ClN_2O$: Cl, 16.16; N, 13.56. Found: Cl, 17.34; N, 13.58.

6-(4-Bromophenyl)-3-pyridazone resulted in 95% yield as white cubes (from ethanol); m.p. 249.5–250.5°.

Anal. Calcd. for $C_{10}H_7BrN_2O$: C, 47.83; H, 2.81; Br, 31.82.[24] Found: C, 47.54; H, 2.70; Br, 31.90.

6-(4-Iodophenyl)-3-pyridazone, white needles (m.p. 173.5–174°) from ethyl acetate, was obtained in 87% yield.

Anal. Calcd. for $C_{10}H_7IN_2O$: C, 40.29; H, 2.37; I, 42.58. Found: C, 40.07; H, 2.20; I, 42.40.

6-(2,4-Dichlorophenyl)-3-pyridazone was formed in 92% yield by the usual method. It crystallized from aqueous ethanol as fibrous white needles, m.p. 216–216.5°.

Anal. Calcd. for $C_{10}H_6Cl_2N_2O$: C, 49.82; H, 2.51; N, 11.62. Found: C, 49.69; H, 2.23; N, 11.52.

6-(3,4-Dichlorophenyl)-3-pyridazone (fibrous white needles from aqueous dioxane; m.p. 256–257°) was isolated in 94% yield.

Anal. Calcd. for $C_{10}H_6Cl_2N_2O$: C, 49.82; H, 2.51; N, 11.62. Found: C, 49.69; H, 2.40; N, 11.69.

II. **6-(3,4-Dichlorophenyl)-4/5-methyl-3-pyridazones (IV) and (V).**—6-(3,4-Dichlorophenyl)-4,5-dihydro-4-methyl-3-pyridazone ((VIII), m.p. 167–168°), was dehydrogenated in the usual manner to produce the desired pyridazone IV in 75% yield. The compound crystallized from ethanol or dioxane in the form of white needles, m.p. 251–251.8°.

Anal. Calcd. for $C_{11}H_8Cl_2N_2O$: C, 51.79; H, 3.16; N, 10.98. Found: C, 51.85; H, 3.35; N, 10.84.

6-(3,4-Dichlorophenyl)-4,5-dihydro-4/5-methyl-3-pyridazone (mixture of isomers from BII, m.p. < 150°) was converted to pyridazone mixture in 70–75% yields. Fractional crystallization from ethanol and from dioxane separated the mixture into the 4-methyl type ((IV), m.p. 250–251°) and 6-(3,4-dichlorophenyl)-5-methyl-3-pyridazone ((V), felted white needles, m.p. 260.2–261°) in a ratio of 1:2.

Anal. Found: C, 52.08; H, 3.31; N, 11.18.

Acknowledgments.—The authors are pleased to make recognition of the friendly interest and encouragement accorded by Dr. C. M. Suter and Dr. J. S. Buck. Mr. M. E. Auerbach, Mr. K. D. Fleischer and their staff in the Analytical Laboratories have performed all analyses reported. We are also grateful to Dr. D. A. Berberian and associates of the Biology Division for the testing of compounds prepared.

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(24) Dumas nitrogen values were not concordant.