Reactions of 2*H*-3,1-Benzoxazine-2,4-(1*H*)dione (Isatoic Anhydride) (1) with Anions of 1,4-Dihydro-5*H*-Pyrazol-5-ones: Synthesis of Pyrazolo[5,1-*b*]quinazolin-9-ones

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Reactions of 2*H*-3,1-benzoxazine-2,4-(1*H*)dione (isatoic anhydride) (**1**) with anions of 1,4-dihydro-5*H*-pyrazol-5-ones (**2**) gave pyrazolo[5,1-*b*]quinazolin-9-ones (**3**) *via* the nucleophilic attack of the anion **2b** rather than **2a**. However, in the case of 5-methoxyisatoic anhydride (**10c**), both products **3e** and **11c** were obtained. A new synthetic method of preparation of 5-(alkylthio)-2-aminobenzoic acids (**18**) was described. These acids (**18**) were used to synthesize a series of substituted pyrazolo[5,1-*b*]quinazolin-9-ones (**3**).

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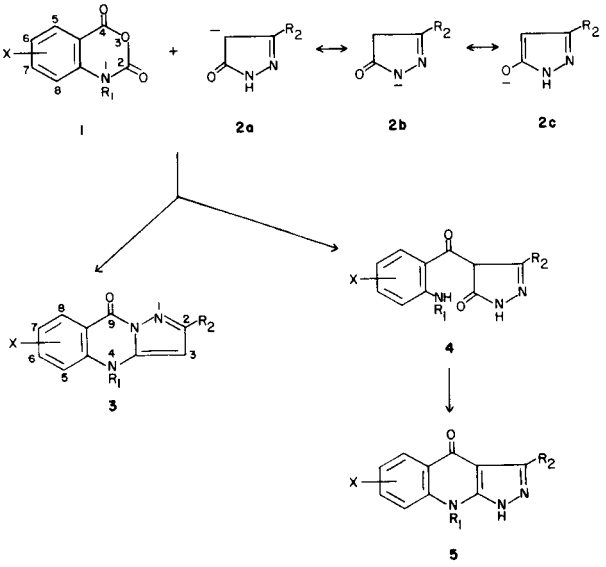
Isatoic anhydride (**1**) readily undergoes a ring opening reaction in presence of various nucleophiles. This facile ring opening reaction of isatoic anhydrides (**1**) has been used for the synthesis of a variety of compounds including several heterocyclic systems (2-7).

As a part of our investigation into the synthesis of novel heterocyclic systems of potential biological interest, we studied the reactions of *N*-alkylisatoic anhydrides (**1**) with 3-substituted-1,4-dihydro-5*H*-pyrazol-5-ones (Scheme I).

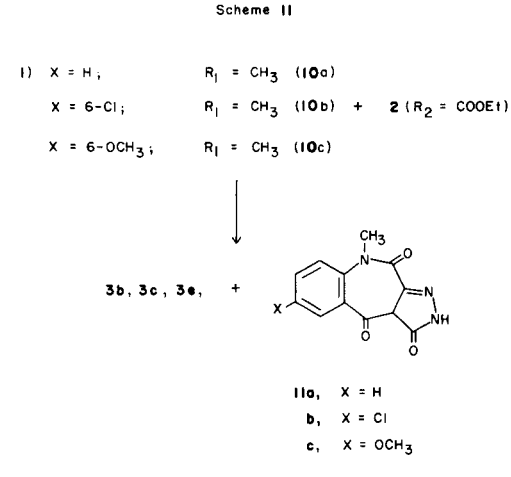
Scheme I



When *N*-methyl-5-chloroisatoic anhydride (**1**; X = 6-Cl; R_1 = CH_3) was allowed to react with anions of 1,4-dihydro-3-methyl-5*H*-pyrazol-5-one, the product obtained was **3a** (Table I) and not **4** or **5** as expected. Apparently, the ambident anion (**2b**) (R_2 = CH_3) reacted with **1** (X = 6-Cl; R_1 = CH_3) to give **3a**. The structure **3** was established from analysis, ir and nmr. The structure **3** was unambiguously proven by methylating the acid **6** (**3**; X = R_1 = H; R_2 = COOH), prepared from the known ester (**7**) (**3**; X = R_1 = H; R_2 = COOEt) (8), to the ester (**8**) (**3**; X = H; R_1 = CH_3; R_2 = $COOCH_3$) which on hydrolysis gave the identical acid (**9**) (**3**; X = H; R_1 = CH_3; R_2 = COOH) prepared *via* the ring opening reaction of **1** (X = H; R_1 = CH_3) with **2** (R_2 = COOEt). The reaction seems to be versatile and was used to prepare a series of compounds of potential biological interest (Table I).

But when 5-methoxy-*N*-methylisatoic anhydride (**10c**) was allowed to react with ethyl 4,5-dihydro-5-oxo-1**H**-pyrazole-3-carboxylate (**2**; R_2 = COOEt) in presence of 50% sodium hydride in *N,N*-dimethylformamide, two products (**3e** and **11c**) were obtained (Scheme II). The structure of compound **3e** was obvious from analysis, ir and nmr. It showed the ester >CO band at 1723 cm^{-1} and a

Scheme II



three proton triplet at 1.65 ppm and a two proton quartet at 4.8 ppm for the ethoxy protons. The compound **11c** gave a red color with ferric chloride solution and showed bands at 3300 (NH), 1660 and 1610 (amide) [formed *via* **4** (X = 5'-OCH_3; R_1 = CH_3; R_2 = COOEt)]. It showed three proton singlets at 3.50 (OCH_3) and 3.85 (N-CH_3) ppm along

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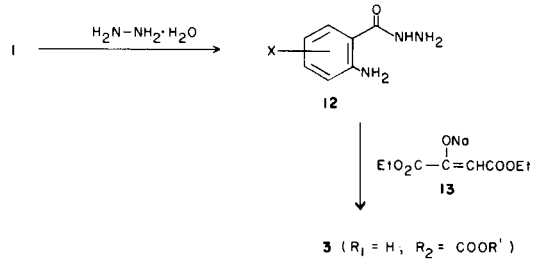
with aromatic protons at 7.40 ppm. It also showed the molecular ion at 273.

Similar reactions of **2** (R = COOEt) with other isatoic anhydrides such as **10a** and **10b** failed to give any 7-membered lactams, **11a** and **11b**.

Attempted extension of the ring opening reaction of *N*-alkyl isatoic anhydride to NH-isatoic anhydrides (**1**, R_1 = H; X = H or 6-Cl) with 1,4-dihydro-5-pyrazol-5-ones (**2**; R_2 = COOEt) failed to give **3** (R_1 = H). The anion of **1** probably reduced the electrophilicity of the carbonyl group and no reaction could be detected.

The NH-series (**3**, R_1 = H) (Table I) was synthesized from substituted 2-aminobenzoic acid hydrazides (**12**) and diethyloxalacetate (**13**) (Scheme III). The substituted 2-aminobenzoic acid hydrazides (**12**) were prepared from the corresponding isatoic anhydrides (**1**). The isatoic anhydrides (**1**) were prepared from the corresponding

Scheme III

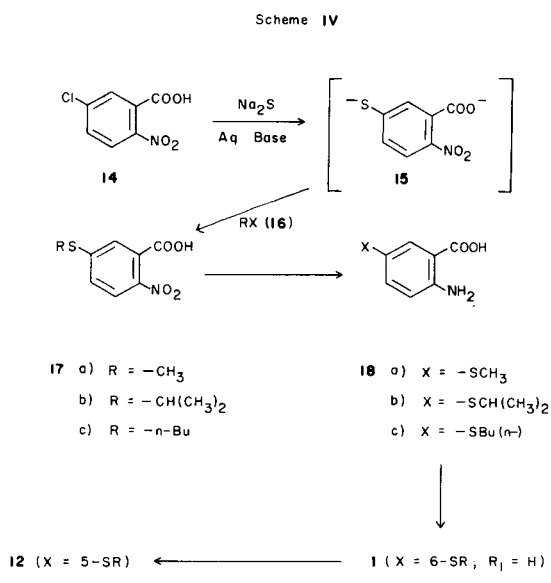


anthranilic acids according to a published procedure (9). The 5-(alkylthio)-2-aminobenzoic acids (**18**) were prepared as follows (Scheme IV).

Reaction of 5-chloro-2-nitrobenzoic acid (**14**) with sodium sulfide in aqueous base gave the intermediate **15** which was alkylated with alkyl halide (**16**) to give **17**. Catalytic reduction of **17** gave **18**.

Methyl 2-amino-3-(tetrahydro-2-thienyl)benzoate (**18d**, methyl ester) was prepared *via* the Gassman Reaction (10) (Scheme V).

Scheme IV



Scheme V

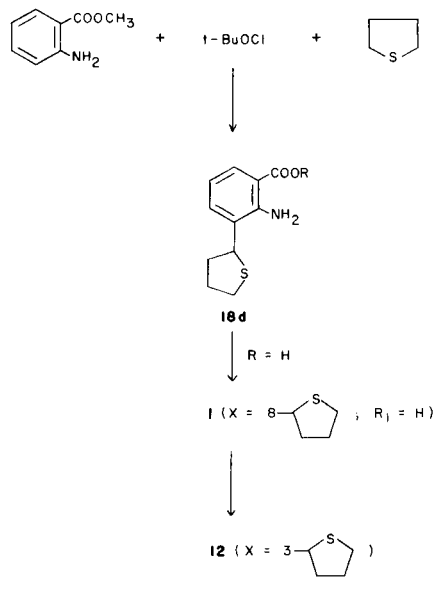


Table I

2-Substituted Pyrazolo[5,1-*b*]quinazolin-9-(1*H*)ones

Compound Number	X	R_1	R_2	Empirical Formula	% Yield	Method	M.p., °C	Elemental Analyses Calcd. C	H	N	Other Elements	Found C	H	N	Other Elements
3a	7-Cl	CH_3	CH_3	$C_{12}H_{10}ClN_3O$	25	A	287-290	58.19	4.07	16.97	Cl, 14.31	57.96	4.07	16.80	Cl, 14.23
3b	H	CH_3	COOEt	$C_{14}H_{13}N_3O_3$	19	A	239-241	61.98	4.83	15.49		61.99	4.72	15.56	
3c	7-Cl	CH_3	COOEt	$C_{14}H_{12}ClN_3O_3$	46	A	272-274	55.00	3.96	13.74	Cl, 11.60	54.80	3.93	13.69	Cl, 11.80
3d	7-F	CH_3	COOEt	$C_{14}H_{12}FN_3O_3$	26	A	288-290	58.13	4.18	14.53	F, 6.57	57.80	4.15	14.38	F, 6.60
3e	7-CH_3O	CH_3	COOEt	$C_{15}H_{15}N_3O_4$	15	B	249-251	59.79	5.02	13.95		59.78	5.04	14.00	
3f	7-Cl	$CH_2C_6H_5$	COOEt	$C_{20}H_{16}ClN_3O_3$	2	A	264-265	62.91	4.22	11.02	Cl, 9.29	62.83	4.20	10.91	Cl, 9.16
3g	7-Cl	CH_2CH_3	COOEt	$C_{13}H_{14}ClN_3O_3$	20	A	256-257	56.35	4.41	13.14	Cl, 11.09	56.44	4.21	13.27	Cl, 11.34
3h	7-CH_3S	H	COOH	$C_{12}H_9N_3O_3S$	29	C	285-289(d)	52.36	3.30	15.26	S, 11.65	52.05	3.22	15.12	S, 11.81
3i	7-CH_3SO	H	COOH	$C_{12}H_9N_3O_4S$	76	D	285-290(d)	49.48	3.11	14.43	S, 11.01	49.20	3.17	14.63	S, 10.60
3j	7-CH_3SO_2	H	COOH	$C_{12}H_9N_3O_5S$	77	E	360-365(d)	46.91	2.95	13.67	S, 10.43	46.73	2.94	13.82	S, 10.28
3k	7-$(CH_3)_3CHS$	H	COOH	$C_{14}H_{13}N_3O_3S$	19	C	275-276(d)	55.43	4.32	13.85	S, 10.57	55.16	4.34	13.82	S, 10.44
3l	7-*n*-BuS	H	COOH	$C_{15}H_{15}N_3O_3S$	27	C	270-271(d)	56.77	4.76	13.24	S, 10.10	56.65	4.73	13.41	S, 10.11
3m	7-*n*-BuSO	H	COOH	$C_{15}H_{15}N_3O_4S \cdot 0.5\ H_2O$	61	D	205-210(d) 260 (d)	52.62	4.71	12.27	S, 9.37	52.70	4.80	12.36	S, 9.61
3n	5- 	H	COOH	$C_{16}H_{19}N_3O_3S \cdot CH_3OH$	6	C	253-255(d)	55.31	4.93	12.09	S, 9.22	55.19	5.03	12.05	S, 9.18

Some of the sulfides (**3**; R_1 = H; R_2 = COOH) were oxidized to the corresponding sulfoxide and sulfones (Table I).

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus or a Mel-Temp apparatus and are uncorrectred. Each analytical sample was homogeneous by tlc and had ir, uv and nmr spectra compatible with its structure. The procedures for the preparation of the reported compounds are listed as methods A-E and may be considered as general methods of preparations. The reported yields for the products obtained were not optimized.

Method A. Ethyl 4,9-Dihydro-4-methyl-9-oxopyrazolo[5,1-*b*]-quinazoline-2-carboxylate (**3b**).

To a suspension of sodium hydride (50% in mineral oil; 5.3 g., 0.11 mole) in *N,N*-dimethylformamide (30 ml.) at −10° under nitrogen was added dropwise a solution of ethyl 4,5-dihydro-5-oxo-1*H*-pyrazole-3-carboxylate (15.6 g., 0.1 mole) in *N,N*-dimethylformamide (65 ml.). When the evolution of hydrogen ceased, the mixture was stirred for 2 hours with temperature gradually reaching 10°. The mixture was cooled back to −10° and a solution of 1-methyl-2*H*-3,1-benzoxazine-2,4-(1*H*)-dione (*N*-methylisatoic anhydride) (90%; 21.6 g., 0.11 mole) in *N,N*-dimethylformamide (150 ml.) was added dropwise to it. The reaction mixture was stirred for 18 hours, gradually attaining the room temperature, and then was heated at 90° for 1 hour. The mixture was then poured into ice-water mixture (3 l.) containing concentrated hydrochloric acid when the product precipitated out (*p*H *ca.* 5.0). The resulting solid was taken up in dichloromethane and the aqueous solution extracted with dichloromethane (4 x 600 ml.). The total dichloromethane extract was washed with water (600 ml.), dried (magnesium sulfate) and the solvent stripped off to give a dark oil. Trituration of the oil with methanol gave a solid. The solid crude product was dissolved in tetrahydrofuran and passed through florisil column to remove the coloring matter. The filtrate was concentrated and then diluted with ethanol. The solution was then slowly concentrated until the product started to crystallize out. The crude product (6.3 g., m.p. 230-240°) thus obtained was recrystallized from dichloromethane-ethanol mixture to yield 5.2 g. (19%) of the product, m.p. 239-241°; ir (nujol): 1710, 1605 cm^{-1}; uv (ethanol): λ max 239 (50,400), 286 (5,800), 293 (7,240), 370 (6,520) mμ; nmr (deuteriochloroform): δ 1.45 (t, 3), 3.75 (s, 3), 4.45 (q, 2), 6.4 (s, 1), 7.0-7.4 (m, 2), 7.6-7.9 (m, 1), 8.3-8.5 (m, 1).

All the compounds (**3a-3n**) in Table I showed the characteristic bands in the ir (nujol) at 1730-1700 and 1600-1630 cm^{-1} for the ester or acid and amide carbonyl group. In the nmr (DMSO-d_6), all of them showed a one proton singlet at 6.40-6.90 ppm for the C_3-proton.

Method B. Ethyl 7-Methoxy-4,9-dihydro-4-methyl-9-oxopyrazolo[5,1-*b*]-quinazoline-2-carboxylate (**3e**) and 3-Hydroxy-6-methoxy-9-methylpyrazolo[3,4-*c*][1]benzazepine-4,10-(2*H*,9*H*)dione (**11c**).

To a suspension of sodium hydride (50% mineral oil, 6.34 g., 0.132 mole) in *N,N*-dimethylformamide (25 ml.), cooled to −10° under nitrogen was added slowly a solution of ethyl 4,5-dihydro-5-oxo-1*H*-pyrazole-3-carboxylate (18.7 g., 0.12 mole) in *N,N*-dimethylformamide (75 ml.). After the evolution of hydrogen ceased, the mixture was stirred for 2 hours when the temperature gradually reached 20°. The reaction mixture was cooled back to −10° and a suspension of 6-methoxy-1-methyl-2*H*-3,1-benzoxazine-2,4-(1*H*)dione (5-methoxy-*N*-methylisatoic anhydride) (**10c**) (27.3 g., 0.132 mole) in *N,N*-dimethylformamide (125 ml.) was added to it slowly. The resulting mixture was stirred at room temperature for 72 hours and then at 90° for 3 hours. The solvent was distilled off and the residue was poured into ice-water mixture (1.5 l.) and the *p*H adjusted to 2 with concentrated hydrochloric acid. The precipitated solid was filtered, washed with water and dried. The crude solid was refluxed with dichloromethane (1800 ml.), and filtered, and dried. The filtrate was worked up as described below. The residue was recrystallized from *N,N*-dimethylformamide-ethanol to give the pure seven-membered lactam (**11c**), yield 2.4 g. (7.3%), m.p. 262-265°; ir (nujol): 3330, 3240, 1660, 1610 cm^{-1}; uv (ethanol): λ max 221 (23,800), 242 (23,200), 350 (5200), mμ; nmr (DMSO-d_6): δ 3.50 (s, 3), 3.85 (s, 3), 7.15-7.60 (m, 3).

Anal. Calcd. for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 56.93; H, 4.01; N, 15.34.

The dichloromethane filtrate from above was evaporated to give a solid residue. The residue was recrystallized from dichloromethane-ethanol mixture to give the desired ester (**3e**), yield 5.2 g. (14.4%), m.p. 249-251°; ir (nujol): 1723, 1697, 1617, 1607 cm^{-1}; uv (ethanol): λ max 240 (48,750), 256 (20,500), 298 (4150), 396 (7100) mμ; nmr (trifluoroacetic acid): δ 1.65 (t, 3), 4.15 (s, 3), 4.25 (s, 3), 4.8 (q, 2), 7.4 (s, 1), 7.85-8.20 (m, 3).

Method C. 4,9-Dihydro-7-(ethylthio)-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic Acid (**3h**).

A mixture of 2-amino-5-(methylthio)benzoic acid hydrazide (2.5 g., 12.7 mmoles) and 90% sodium diethyloxalacetate (3.27 g., 14 mmoles) in water (50 ml.) was heated under reflux for 2 hours. Sodium carbonate (1.5 g., 14 mmoles) solution in water (15 ml.) was added to the reaction mixture and the heating was continued for another hour. The reaction mixture was cooled, carefully acidified with concentrated hydrochloric acid (4 ml.) and the resulting yellow precipitate was filtered, washed and dried. The product was recrystallized from methanol-water, yield 1.0 g., m.p. 285-289° dec.

Method D. 4,9-Dihydro-7-(methylsulfinyl)-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic Acid (**3i**).

A mixture of 4,9-dihydro-7-(methylthio)-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acid (5.5 g., 0.02 mole) and 1*N* sodium hydroxide solution (25 ml.) in water (500 ml.) was chilled to 12° and a solution of sodium metaperiodate (4.28 g., 0.02 mole) in water (150 ml.) was added. The reaction mixture was stirred at room temperature for 4 hours and the resulting solution was cooled and treated with 1*N* hydrochloric acid (30 ml.). The greenish precipitate was filtered, washed and recrystallized from *N,N*-dimethylformamide-methanol, yield 4.4 g. (76%); m.p. 285-290° dec.; ir (potassium bromide): 1715, 1680, 1640, 1190, 1070 cm^{-1}; uv (methanol): λ max 242 (37,400), 270 (12,400), 301 (17,600), 363 (4,550) mμ; nmr (DMSO-d_6): δ 2.8 (s, 3), 6.4 (s, 1), 7.4-8.4 (m, 3).

Method E. 4,9-Dihydro-7-(methylsulfonyl)-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic Acid (**3j**).

A mixture of 4,9-dihydro-7-(methylthio)-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acid (1.1 g., 4 mmoles), glacial acetic acid and 30% hydrogen peroxide (3 ml.) was heated under reflux for 1 hour and then stirred at room temperature overnight. The tan solid was filtered off and recrystallized from *N,N*-dimethylformamide-ether, yield 0.95 (77%); m.p. 360-365° dec.; ir (potassium bromide): 1710, 1630, 1305, 1130 cm^{-1}; nmr (DMSO-d_6): δ 3.3 (s, 3), 6.5 (s, 1), 7.5-8.6 (m, 3).

Methyl 4,9-Dihydro-4-methyl-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylate (**8**).

A mixture of 4,9-dihydro-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acid (prepared from the known ester **6** (7) (2.29 g., 0.01 mole), anhydrous potassium carbonate (5.52 g., 0.04 mole) and methyl iodide (34.2 g., 0.24 mole) in *N,N*-dimethylformamide (100 ml.) was stirred at room temperature for 3 days. Water was added and the white solid was filtered off to give the methyl ester (**8**; 2.2 g., 86%), m.p. 287-289° dec.; ir (potassium bromide): 1728, 1703; 1606 cm^{-1}; uv (ethanol): λ max 240 (50,800), 292 (7,600), 370 (6,650) mμ; nmr (DMSO-d_6): δ 3.85 (s, 3), 3.93 (s, 3), 6.90 (s, 1), 7.30-7.90 (m, 3), 8.35 (d, 1).

Anal. Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.69; H, 4.31; N, 16.34. Found: C, 60.50; H, 4.29; N, 16.29.

4,9-Dihydro-4-methyl-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic Acid (**9**).

A mixture of ethyl 4,9-dihydro-4-methyl-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylate (**3b**; 2.9 g., 0.011 mole), 1*N* sodium hydroxide solution (25 ml.) and methanol (200 ml.) was refluxed for 2.0 hours until a clear solution was formed. The methanol was distilled off and the residual

solution diluted with water and acidified. The precipitated acid was filtered, washed and recrystallized from *N,N*-dimethylformamide-methanol mixture, yield 2.10 (81%), m.p. 265-266°; ir (nujol): 1725, 1710, 1620, 1610 cm^{-1}; uv (ethanol): λ max 240 (45,750), 289 (8,250), 369 (6,000) mμ; nmr (DMSO-d_6): δ 3.85 (s, 3), 6.75 (s, 1), 8.1 (b, 4), 13.2 (b, 1-exchangeable with deuterium oxide).

Anal. Calcd. for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.17; H, 3.80; N, 17.39.

Similarly, the methyl ester (**8**; 1.98 g.) was hydrolysed to give **9** (1.9 g., 100%), m.p. 265-266°. It was identical in all respects with the sample above.

Preparation of Intermediates.

(a) 5-(Methylthio)-2-nitrobenzoic Acid (**17a**).

5-Chloro-2-nitrobenzoic acid (100.8 g., 0.5 mole) was dissolved in water (1.0 l.) and 4*N* sodium hydroxide solution (83 ml.) (*p*H 7.5). A solution of sodium sulfide (132 g., 0.55 mole) in water (300 ml.) was added and the mixture was heated at 50-55° for 2.5 hours. The reaction mixture was then treated with 20% sodium hydroxide solution (100 ml.) and dimethyl sulfate (126.2 g., 1.0 mole) and was heated under reflux for 1.0 hour. On cooling and acidification with 4*N* hydrochloric acid (160 ml.), the product precipitated out as a yellow solid (101.5 g.), which was recrystallized from ether, m.p. 175-178°.; ir (nujol): 1710, 1560, 1510, 1340 cm^{-1}; nmr (DMSO-d_6): δ 2.4 (s, 3), 7.3 (m, 2), 7.8 (d, 1).

Anal. Calcd. for $C_8H_7NO_4S$: C, 45.07; H, 3.31; N, 6.57; S, 15.04. Found: C, 44.84; H, 3.35; N, 6.51; S, 15.14.

(b) 5-[(1-Methylethyl)thio]-2-nitrobenzoic Acid (**17b**).

The compound (**17b**) was prepared from 5-chloro-2-nitrobenzoic acid (**14**) (20.2 g., 0.1 mole), 1.05*N* sodium hydroxide solution (315 ml.), sodium sulfide (26.4 g., 0.11 mole) in water (100 ml.) and isopropyl bromide (32.75 g., 0.266 mole) by the procedure of example, **17a**, yield 25 g. (98%), m.p. 133-139°; ir (nujol): 1710, 1600, 1570, 1340 cm^{-1}; nmr (deuteriochloroform): δ 1.4 (d, 6), 3.7 (m, 1), 7.6 (m, 3).

Anal. Calcd. for $C_{10}H_{11}NO_4S$: C, 49.78; H, 4.60; N, 5.81; S, 13.29. Found: C, 49.81; H, 4.39; N, 5.70; S, 13.04.

(c) 5-(Butylthio)-2-nitrobenzoic Acid (**17c**).

The compound (**17c**) was prepared from 5-chloro-2-nitrobenzoic acid (20.2 g., 0.1 mole), 0.87*N* sodium hydroxide solution (380 ml.), sodium sulfide (26.4 g., 0.11 mole) and 1-bromobutane (41.1 g., 0.3 mole) at 80° for 4.0 hours. The reaction mixture was acidified with concentrated hydrochloric acid, extracted with dichloromethane (3 x 200 ml.) and the extracts were dried over sodium sulfate. The dichloromethane was evaporated and the yellow solid residue was recrystallized from a mixture of ether and cyclohexane, yield 17.0 g. (67%), m.p. 105-110°; ir (nujol): 1710, 1560, 1500, 1330 cm^{-1}; nmr (deuteriochloroform): δ 1.0 (t, 3), 1.70 (m, 4), 3.1 (t, 2), 7.4 (m, 2), 7.8 (d, 1), 9.6 (b, 1).

Anal. Calcd. for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49; S, 12.56. Found: C, 51.81; H, 5.13; N, 5.34; S, 12.42.

(d) 5-(Methylthio)-2-aminobenzoic Acid (**18a**).

A mixture of 5-(methylthio)-2-nitrobenzoic acid (25.4 g., 0.119 mole), methanol (200 ml.) and Raney nickel (2 g.) was shaken in an atmosphere of hydrogen at 50 lb. of pressure until the theoretical amount of hydrogen was absorbed. The catalyst was filtered off and the filtrate evaporated to dryness. The residue was recrystallized from ether-isopropyl ether, yield 7.6 g., m.p. 145-150°; ir (nujol): 3460, 3340, 1665, 1610 cm^{-1}; nmr (deuteriochloroform): δ 2.4 (s, 3), 6.7 (d, 1), 7.3 (m, 1), 8 (m, 1).

Anal. Calcd. for $C_8H_9NO_2S$: C, 52.44; H, 4.95; N, 7.64; S, 17.50. Found: C, 52.22; H, 4.99; N, 7.38; S, 17.78.

(e) 5-(Butylthio)-2-aminobenzoic Acid (**18c**).

Catalytic hydrogenation of 5-(butylthio)-2-nitrobenzoic acid (10.6 g., 0.042 mole) in methanol (120 ml.) in presence of Raney nickel (1 g.) by the procedure of example **18a** gave 5-(butylthio)-2-aminobenzoic acid (8.95 g.), m.p. 69-72°; ir (nujol): 3420, 3310, 1675 cm^{-1}; nmr (deuteriochloroform): δ 0.9 (m, 3), 1.5 (m, 4), 2.8 (t, 2), 6.7 (d, 1), 7.3-8.1 (m, 5).

Anal. Calcd. for $C_{11}H_{15}NO_2S$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.48; H, 6.78, N, 6.23.

(f) Methyl 2-Amino-3-(tetrahydro-2-thienyl)benzoate (**18d**, Methyl Ester).

A solution of methyl 2-aminobenzoate (75.5 g., 0.5 mole) in dichloromethane (1.0 l.) was cooled to −70° and a solution of *tert*-butyl hypochlorite (54 g., 0.5 mole) in dichloromethane (150 ml.) was added slowly keeping the temperature at −70°. The resultant methyl 2-(chloroamino)-benzoate solution was stirred for 1.0 hour and then tetrahydrothiophene (110 ml.) was added at such a rate as to maintain the exotherm to less than 10°. The dark solution was stirred at −70° for 2.0 hours, triethylamine (125 ml.) was added dropwise, and the solution was stirred for 24 hours. The solvents were removed and the residue was diluted with dichloromethane, washed with 1*N* sodium hydroxide solution, water and dried. Removal of solvents gave an oil. Unreacted methyl 2-aminobenzoate was removed under reduced pressure (b.p. 95-100°/0.35 mm) at bath temperature at 150° and the residue was dissolved in dichloromethane, partially chromatographed through silica gel and the solid residue was recrystallized from methanol, yield 27.0 g., m.p. 75-79°; ir (potassium bromide): 3480, 3380, 1700, 1620 cm^{-1}; nmr (deuteriochloroform): δ 2.0-2.4 (m, 4), 3.1 (m, 2), 3.8 (s, 3), 4.5 (t, 1), 6.3 (b, 2, exchangeable) 6.75 (t, 1), 7.4 (m, 1), 7.85 (m, 1).

Anal. Calcd. for $C_{12}H_{15}NO_2S$: C, 60.75; H, 6.37; N, 5.90; S, 13.49. Found: C, 60.57; H, 6.34; N, 5.85; S, 13.50.

(g) 5-(Methylthio)-2-aminobenzoic Acid Hydrazide (**12**, X = 5-CH_3S-).

5-(Methylthio)-2-nitrobenzoic acid (53.25 g., 0.25 mole) was added to a solution of stannous chloride (225.6 g., 1.0 mole) in concentrated hydrochloric acid (340 ml.) and the reaction mixture was brought to 110° and then cooled and concentrated. The concentrate was brought to *p*H 13 cautiously with 4*N* sodium hydroxide solution. The mixture was then filtered through supercel and the *p*H of the filtrate was adjusted to 6.7 and refiltered. The filtrate was cooled and treated with 12.5% phosgene in benzene solution (400 ml.) to give 6-(methylthio)-2*H*-3,1-benzoxazine-2,4-(1*H*)dione (5-methylthioisatoic anhydride) (**1**, X = 6-SCH_3; R_1 = H) (30.6 g.), m.p. 216-218°; ir (nujol): 1770, 1760, 1700 cm^{-1}. This was used in the next step as follows.

6-(Methylthio)-2*H*-3,1-benzoxazine-2,4-(1*H*)dione (**1**, X = 6-CH_3S; R_1 = H) (25.11 g., 0.12 mole) was added to a cold solution of 54.4% hydrazine (75 ml.) in water (75 ml.). After stirring at room temperature overnight, the white solid was filtered, washed with cold water and dried, yield 21.3 g. (90%), m.p. 124-127°; ir (nujol): 3420, 3325, 1630, 1600 cm^{-1}; nmr (DMSO-d_6): δ 2.3 (s, 3), 4.34 (b, 5), 6.6 (d, 1), 7.15 (m, 1), 7.45 (s, 1).

Anal. Calcd. for $C_8H_{11}N_3OS$: C, 48.72; H, 5.62; N, 21.31. Found: C, 49.01; H, 5.88; N, 21.48.

(h) 2-Amino-5-[(1-methylethyl)thio]benzoic Acid Hydrazide (**12**; X = 5-$(CH_3)_2CHS$-).

Following the procedure of example g, 5-[(1-methylethyl)thio]-2-nitrobenzoic acid (12.05 g., 0.05 mole) was reduced with stannous chloride (45.2 g., 0.2 mole) and concentrated hydrochloric acid (70 ml.) at 85° for 1.0 hour. The reaction mixture containing the corresponding anthranilic acid was treated with 12.5% phosgene in benzene (100 ml.) at room temperature to give 6-[(1-methylethyl)thio]-2*H*-3,1-benzoxazine-2,4(1H)-dione (5-isopropylthioisatoic anhydride), yield 7.45 g. (63%), m.p. 219-221° dec., ir (nujol): 1790, 1765, 1700 cm^{-1}.

The crude isatoic anhydride (**1**, X = 6-$(CH_3)_2CHS$; R_1 = H) (9.1 g., 0.038 mole) obtained above was converted to the corresponding benzoic acid hydrazide (**12**, X = 5-$(CH_3)_2CHS$-) by reacting with cold 27.2% aqueous hydrazine solution (50 ml.) at room temperature overnight. The white solid was filtered off, washed with cold water and dried, yield 8.05 g. (94%), m.p. 110-115°; ir (nujol): 3440, 3280, 1645, 1600 cm^{-1}; nmr deuteriochloroform): δ 1.15 (d, 6), 3.1 (m, 1), 4.70 (b, ~5, exchangeable with deuterium oxide 6.55 (d, 1), 7.35 (m, 2).

Anal. Calcd. for $C_{10}H_{15}N_3OS$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.27; H, 7.01; N, 18.61.

(i) 6-(Butylthio)-2*H*-3,1-benzoxazine-2,4-(1*H*)dione. (5-*n*-Butylthioisatoic Anhydride) (**1**, X = 6-*n*-BuS, R_1 = H).

A solution of phosgene (12.5%) in benzene (40 g., 0.05 mole) was added to a cooled (5°) solution of 2-amino-5-(butylthio)benzoic acid (8.9 g., 0.0395 mole) in dioxane (150 ml.) and benzene (80 ml.). The mixture was stirred at room temperature over-night and the pale green crystals were filtered off and dried, yield 6.85 g., m.p. 196-200°; ir (nujol): 1770, 1730 cm^{-1}; nmr (DMSO-d_6): δ 0.85 (t, 3), 1.45 (m, 4), 3.0 (t, 2), 7.15 (d, 1), 7.75 (m, 2), 11.75 (s, 1, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.23; H, 5.26; N, 5.49.

(j) 2-Amino-5-(butylthio)benzoic Acid Hydrazide. (**12**; X = 5-*n*-BuS).

6-(Butylthio)-2*H*-3,1-benzoxazine-2,4-(1*H*)dione (**1**, X = 6-*n*-BuS, R_1 = H) (8.65 g., 0.034 mole) was added to a cold mixture of 54.4% hydrazine (25 ml.) and water (25 ml.) and stirred at room temperature overnight. The white solid was filtered, washed, and dried, yield 7.68 g. (94%), m.p. 92-95°; ir (nujol): 3430, 3400, 3275, 1620 cm^{-1}; nmr (DMSO-d_6): δ 0.9 (t, 3), 1.4 (m, 4), 2.8 (t, 2), 4.35 (s, 2), 6.2 (s, 2), 6.65 (d, 1), 7.15 (m, 1), 7.45 (s, 1), 9.55 (b, 1).

Anal. Calcd. for $C_{11}H_{17}N_3OS$: C, 55.20; H, 7.16; N, 17.56; S, 13.40. Found: C, 54.91; H, 7.02; N, 17.67; S, 13.36.

2-Amino-3-(tetrahydro-2-thienyl)benzoic Acid Hydrazide (**12**, X = ).

A mixture of methyl 2-amino-3-(tetrahydro-2-thienyl)benzoate (**18d**, methyl ester) (10 g., 0.042 mole) and 0.2*N* sodium hydroxide solution (210 ml.) was refluxed for 4.0 hours, cooled, filtered and the filtrate was treated with 12.5% phosgene solution in benzene (36 ml.) in an ice bath. The mixture was stirred for 2.0 hours and the product, 8-(tetrahydro-2-thienyl)-2*H*-3,1-benzoxazine-2,4-(1*H*)dione (**1**, X =  ; R_1 = H), was filtered off and dried *in vacuo*, yield 6.0 g., m.p. 195-199° dec.

The crude isatoic anhydride (6.0 g.) from above was added slowly to a mixture of 85% hydrazine hydrate (25 ml.) and water (25 ml.) and the reaction mixture stirred overnight. The white crystalline hydrazide was filtered, washed and dried, yield 5.0 g., m.p. 123-127°; ir (potassium bromide): 3450, 3300, 1620 cm^{-1}; nmr (deuteriochloroform): δ 2.3 (m, 4), 3.1 (m, 2), 4.0 (b, 2), 4.5 (t, 1), 5.85 (b, 2), 6.7 (t, 1), 7.35 (m, 3).

Anal. Calcd. for $C_{11}H_{15}N_3OS$: C, 55.68; H, 6.37; N, 17.71; S, 13.49. Found: C, 55.16; H, 6.35; N, 17.47; S, 13.37.

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(1) The numbering system shown in structure **1** is that adapted by Chemical Abstracts Service and it varies from earlier numbering where carbonyl attached carbon was numbered as 1 and numbered clockwise.

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