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Synthesis of 1-Methyl-3H-1,4-benzodiazepine-2,5(1H,4H)-dione and Derivatives

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Derivatives of 1-methyl-3H-1,4-benzodiazepine-2,5(1H,4H)-dione were synthesized by ring closure of substituted 2[(N-chloroacetyl-N-methyl)amino]benzamides with sodium methoxide in methanol.

Until recently there were very few reports in the literature about 1,4-benzodiazepine derivatives (1,2). Because of the recent discovery of the psychopharmacological properties of the 1,4-benzodiazepines (3), there is now more interest in this area, as shown by a large number of publications by Sternbach and other workers since 1961 (4).

This paper describes the synthesis of 1-methyl-3H-1,4-benzodiazepine-2,5(1H,4H)-dione and derivatives, and the reduction with lithium aluminum hydride to 4-substituted-1-methyl-1H-2,3,4,5-tetrahydro-1,4-benzodiazepines. Recently, 3H-1,4-benzodiazepine-2,5(1H,4H)-dione was prepared by ring closure of 2-aminohippuric acid piperidide with acetic acid (5).

N-Methylisatoic anhydride (Ia), 5-chloro-N-methylisatoic anhydride (Ib), and 4-chloro-N-methylisatoic anhydride (Ic) (6) were allowed to react with various amines to yield the substituted 2-(methylamino)benzamides (IIa-k, Table I). When compounds IIa-k were treated with chloroacetyl chloride in acetic acid or in a mixture of equal volume of acetic acid and saturated aqueous sodium acetate, the N-chloroacetyl derivatives (IIIa-k, Table II) were obtained. The cyclization to the substituted 1-methyl-3H-1,4-benzodiazepine-2,5(1H,4H)-diones (IVa-k, Table III) was effected by heating the N-chloroacetyl derivatives with one equivalent of sodium methoxide in methanol. Several 4-substituted-1-methyl-3H-1,4-benzodiazepine-2,5(1H,4H)-diones were reduced to the 4-substituted-1-methyl-1H-2,3,4,5-tetrahydro-1,4-benzodiazepines (Va-e, Table IV) by the use of lithium aluminum hydride.

Methyl 2-[(N-chloroacetyl-N-methyl)amino]benzoate (VI) was obtained by the reaction of methyl 2-(methylamino)benzoate with chloroacetyl chloride in the presence of toluene and 10% aqueous sodium hydroxide. Treatment of VI with ammonia yielded 1-methyl-3H-1,4-benzodiazepine-2,5(1H,4H)-dione (VIIa). When VI was heated with benzylamine, 4-benzyl-1-methyl-3H-1,4-benzodiazepine-2,5(1H,4H)-dione (VIIb) was formed. An attempt to convert VIIb to VIIa by the use of hydrogen and palladium failed.

When 2-[(N-chloroacetyl-N-methyl)amino]-N-methylbenzamide (IIIa) was refluxed with pyridine, 1,3-dimethyl-2,4(1H,3H)-quinazolinedione (VIIIa) was obtained. On heating 2-[(N-chloroacetyl-N-methyl)amino]benzanilide (IIIb) with pyridine, 1-methyl-3-phenyl-2,4(1H,3H)-quinazolinedione (VIIIb) was isolated.

EXPERIMENTAL (9)

4-Chloro-2-(methylamino)-N-methylbenzamide (IIg).

A mixture of 10.6 g. (0.05 mole) of 4-chloro-N-methylisatoic anhydride and 31 ml. (0.15 mole) of 15% aqueous methylamine was heated, with stirring, for 1 hr. on a steam bath. The mixture was cooled in an ice bath and the product was filtered.

Compounds IIa and IIi were prepared in the same manner.

4-Chloro-2-(methylamino)benzanilide (IIh).

A mixture of 10.6 g. (0.05 mole) of 4-chloro-N-methylisatoic anhydride, 4.7 g. (0.05 mole) of aniline, 0.15 g. of powdered sodium hydroxide, and 50 ml. of *p*-dioxane was heated, with stirring, in an oil bath, maintained at 70-80° for 2 hr., and then at 100° for 2 hr. The mixture was diluted with water and cooled in an ice bath. The product was filtered and recrystallized.

Compounds (Table I) were prepared in the same manner from the required isatoic anhydride and the arylamine.

2-[(N-Chloroacetyl-N-methyl)amino]-N-methylbenzamide (IIIa).

Chloroacetyl chloride (8.5 g., 0.075 mole) was added, dropwise, to a stirred, ice-water cooled mixture of 8.2 g. (0.05 mole) of 2-(methylamino)-N-methylbenzamide in 15 ml. of acetic acid and 15 ml. of saturated aqueous sodium acetate. After 3 hr., the mixture was diluted with water and the product was filtered.

Compounds IIIg and IIIi were prepared in the same manner omitting sodium acetate and, after dilution with water, the mixture was refrigerated for several days and the product was collected.

2-[(N-Chloroacetyl-N-methyl)amino]benzanilide (IIIb).

To a stirred solution of 11.3 g. (0.05 mole) of 2-(methylamino)-benzanilide in 150 ml. of acetic acid, there was added, dropwise, 8.5 g. (0.075 mole) of chloroacetyl chloride. The mixture was stirred for 1 hr. at room temperature, and for 1 hr. at steam bath temperature. After the addition of 500 ml. of water, the suspension was refrigerated overnight. The product was filtered and recrystallized.

Other compounds (Table II) were prepared in the same way.

1,4-Dimethyl-3H-1,4-benzodiazepine-2,5(1H,4H)-dione (IVa).

2-[(N-Chloroacetyl-N-methyl)amino]-N-methylbenzamide (2.4 g., 0.01 mole) was added to a stirred solution of 0.23 g. (0.01 g. atom) of sodium in 100 ml. of methanol. The mixture was refluxed for 4 hr. on a steam bath, and evaporated to dryness *in vacuo*. The residue was washed with water and recrystallized.

Compounds IVb-k (Table III) were prepared in the same manner.

1-Methyl-4-phenyl-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine (Va).

A suspension of 5.3 g. (0.02 mole) of finely powdered 1-methyl-4-phenyl-3H-1,4-benzodiazepine-2,5(1H,4H)-dione in 100 ml. of absolute ether was added, gradually, to a stirred mixture of 2 g. of lithium aluminum hydride in 300 ml. of absolute ether. The mixture was refluxed for 48 hr. After cooling, 2 ml. of water was added, dropwise, followed by 2 ml. of 40% aqueous sodium hydroxide. After filtration, the filtrate was dried over anhydrous sodium sulfate, evaporated, and the residue was distilled *in vacuo*.

Compounds Vb-e (Table IV) were prepared in the same manner but the residue was recrystallized from an appropriate solvent.

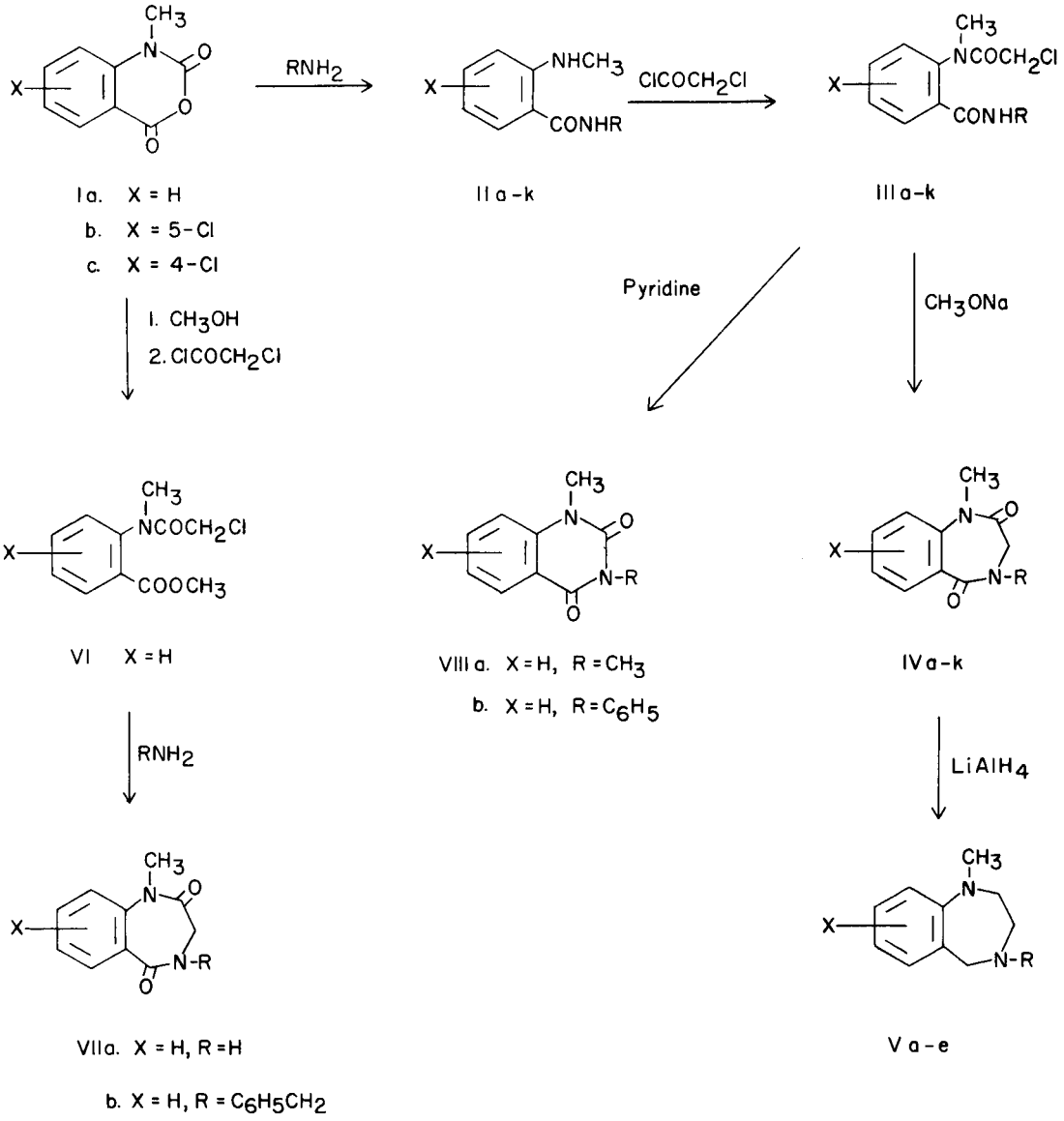
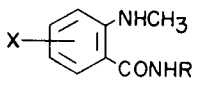


TABLE I

Substituted 2-(Methylamino)benzamides

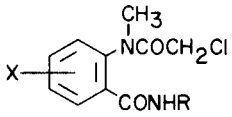


Compound	X	R	M.P.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
IIa (a, b)	H	CH_3	67-68	70	$C_9H_{12}N_2O$	65.83	66.05	7.37	7.32	17.06	17.21
IIb (c)	H	C_6H_5	124-125	75	$C_{14}H_{14}N_2O$	74.30	75.08	6.23	6.31	12.39	12.87
IIc	H	4-ClC_6H_4	134-135	64	$C_{14}H_{13}ClN_2O$	64.50	64.39	5.03	5.14	10.75	10.77
IId	H	2-$CH_3OC_6H_4$	93-94	63	$C_{15}H_{16}N_2O_2$	70.29	70.35	6.29	6.27	10.93	10.99
IIe	H	4-$CH_3OC_6H_4$	122-123	77	$C_{15}H_{16}N_2O_2$	70.29	70.39	6.29	6.25	10.93	10.90
IIf	H	3,4,5-$(CH_3O)_3C_6H_2$	182-183	79	$C_{17}H_{20}N_2O_4$	64.54	64.36	6.37	6.48	8.86	8.90
IIg	4-Cl	CH_3	86-87	94	$C_9H_{11}ClN_2O$	54.41	54.41	5.58	5.47	14.10	13.98
IIh	4-Cl	C_6H_5	148-149	85	$C_{14}H_{13}ClN_2O$	64.50	64.47	5.03	5.21	10.75	10.92
IIi	5-Cl	CH_3	95-97	81	$C_9H_{11}ClN_2O$	54.41	54.59	5.58	5.35	14.10	13.99
IIj	5-Cl	C_6H_5	183-184	74	$C_{14}H_{13}ClN_2O$	64.50	64.42	5.03	4.86	10.75	10.76
IIk	5-Cl	4-$CH_3OC_6H_4$	181-182	69	$C_{15}H_{15}ClN_2O_2$	61.96	62.31	5.20	5.28	9.64	9.65

(a) Compound IIa was recrystallized from cyclohexane; IIb and IIg from benzene-petroleum ether (b.p. 60-68°); IIc from ethanol-petroleum ether (b.p. 60-68°); IId from ethanol; IIe and IIh from aqueous ethanol; IIf, IIj, and IIk from 95% ethanol; IIi from petroleum ether (b.p. 60-68°). (b) Reference 7. (c) Reference 8.

TABLE II

Substituted 2-[(N-Chloroacetyl-N-methyl)amino]benzamides

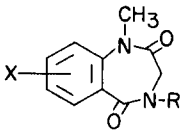


Compound	X	R	M. P.	Yield, %,	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
IIIa (a)	H	CH_3	116-117	68	$C_{11}H_{13}ClN_2O_2$	54.89	54.55	5.45	5.30	11.64	12.02
IIIb	H	C_6H_5	184-185	87	$C_{16}H_{15}ClN_2O_2$	63.47	63.43	4.99	5.13	9.25	9.38
IIIc	H	$4\text{-}ClC_6H_4$	161-162	79	$C_{16}H_{14}Cl_2N_2O_2$	56.99	57.17	4.19	4.15		
IIId	H	$2\text{-}CH_3OC_6H_4$	96-98	63	$C_{17}H_{17}ClN_2O_3$	61.35	61.42	5.15	5.14	8.42	8.50
IIIe	H	$4\text{-}CH_3OC_6H_4$	156-157	74	$C_{17}H_{17}ClN_2O_3$	61.35	61.30	5.15	5.11	8.42	8.43
IIIf	H	$3,4,5\text{-}(CH_3O)_3C_6H_2$	167-168	77	$C_{19}H_{21}ClN_2O_5$	58.08	58.22	5.39	5.54	7.13	7.32
IIIg	4-Cl	CH_3	80-82	61	$C_{11}H_{12}Cl_2N_2O_2$	48.02	47.71	4.40	4.37	10.18	9.78
IIIh	4-Cl	C_6H_5	194-195	83	$C_{16}H_{14}Cl_2N_2O_2$	56.99	56.78	4.19	4.05	8.31	8.43
IIIi	5-Cl	CH_3	201-202	40	$C_{11}H_{12}Cl_2N_2O_2$	48.02	47.74	4.40	4.17	10.18	10.78
IIIj	5-Cl	C_6H_5	173-174	75	$C_{16}H_{14}Cl_2N_2O_2$	56.99	57.04	4.19	4.00	8.31	8.17
IIIk	5-Cl	$4\text{-}CH_3OC_6H_4$	148-150	86	$C_{17}H_{16}Cl_2N_2O_3$	55.74	55.86	4.39	4.82	7.63	7.43

(a) Compound IIIa was recrystallized from ethanol-ether; IIIb, IIIc, IIIe, IIIf, IIIh, IIIj, and IIIk from isopropyl alcohol; IIId from isopropyl alcohol-isopropyl ether; IIIg and IIIi from ethanol-petroleum ether (b.p. 60-68°).

TABLE III

Substituted 1-Methyl-3H-1, 4-benzodiazepine-2, 5(1H, 4H)-diones

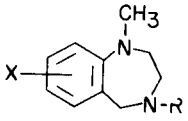


Compound	X	R	M. P.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
IVa (a)	H	CH_3	146-147	74	$C_{11}H_{12}N_2O_2$	64.69	64.88	5.92	6.06	13.72	13.75
IVb	H	C_6H_5	181-182	83	$C_{16}H_{14}N_2O_2$	72.16	72.35	5.30	5.41	10.52	10.73
IVc	H	$4\text{-}ClC_6H_4$	120-121	69	$C_{16}H_{13}ClN_2O_2$	63.90	63.99	4.36	4.69	9.32	9.20
IVd	H	$2\text{-}CH_3OC_6H_4$	237-238	92	$C_{17}H_{16}N_2O_3$	68.90	68.82	5.44	5.64	9.45	9.27
IVe	H	$4\text{-}CH_3OC_6H_4$	190-191	84	$C_{17}H_{16}N_2O_3$	68.90	68.84	5.44	5.68	9.45	9.43
IVf	H	$3,4,5\text{-}(CH_3O)_3C_6H_2$	169-170	85	$C_{19}H_{20}N_2O_5$	64.04	64.20	5.66	5.74	7.86	8.03
IVg	8-Cl	CH_3	193-194	70	$C_{11}H_{11}ClN_2O_2$	55.35	55.52	4.65	4.76	11.76	11.76
IVh	8-Cl	C_6H_5	190-191	83	$C_{16}H_{13}ClN_2O_2$	63.90	63.69	4.36	4.16	9.32	9.41
IVi	7-Cl	CH_3	111-112	73	$C_{11}H_{11}ClN_2O_2$	55.35	55.32	4.65	4.96	11.74	11.51
IVj	7-Cl	C_6H_5	136-137	80	$C_{16}H_{13}ClN_2O_2$	63.90	63.92	4.36	4.46	9.32	9.32
IVk	7-Cl	$4\text{-}CH_3OC_6H_4$	140-141	74	$C_{17}H_{15}ClN_2O_3$	61.73	61.94	4.57	4.54	8.47	8.30

(a) Compounds IVa and IVf were recrystallized from ethanol with the use of Norite; IVb and IVh from methanol; IVc and IVe from methanol with the use of Norite; IVd from Methyl Cellosolve; IVg and IVi from 95% ethanol; IVj and IVk from isopropyl alcohol with the use of Norite.

TABLE IV

4-Substituted 1-Methyl-1H-2, 3, 4, 5-tetrahydro-1, 4-benzodiazepines



Compound	X	R	M. P. B. P. (mm.)	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Va	H	C_6H_5	160-162 (0.3)	57	$C_{16}H_{18}N_2$	80.63	80.55	7.61	7.94	11.75	11.72
Vb (a)	H	$2\text{-}CH_3OC_6H_4$	78-79	64	$C_{17}H_{20}N_2O$	76.08	76.30	7.51	7.53	10.44	10.58
Vc	H	$4\text{-}CH_3OC_6H_4$	64-65	75	$C_{17}H_{20}N_2O$	76.08	75.92	7.51	7.39	10.44	10.64
Vd	H	$3,4,5\text{-}(CH_3O)_3C_6H_2$	113-114	62	$C_{19}H_{24}N_2O_3$	69.51	69.52	7.37	7.30	8.53	8.63
Ve	7-Cl	$4\text{-}CH_3OC_6H_4$	87-88	58	$C_{17}H_{19}ClN_2O$	67.43	67.63	6.32	6.35	9.26	9.10

(a) Compounds Vb, Vc, Vd, and Ve were recrystallized from petroleum ether (b.p. 60-68°).

Methyl 2-[(N-chloroacetyl-N-methyl)amino]benzoate (VI).

Chloroacetyl chloride (56.5 g., 0.5 mole) was added, dropwise, to a stirred, ice-water cooled mixture of 46.5 g. (0.28 mole) of methyl 2-(methylamino)benzoate (8) in 280 ml. of toluene and 280 ml. of 10% aqueous sodium hydroxide. Toward the end of the addition, a further quantity of 20 ml. of sodium hydroxide was added, and the mixture was stirred for 3 hr. at room temperature. The toluene layer was separated, washed with water, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled to give 42.5 g. of the product, b.p. 134-138°/0.15 mm. (Yield: 63%).

Anal. Calcd. for $C_{11}H_{12}ClNO_3$: C, 54.67; H, 5.01; N, 5.80. Found: C, 54.89; H, 4.93; N, 6.02.

1-Methyl-3H-1,4-benzodiazepine-2,5(1H,4H)-dione (VIIa).

A slow stream of ammonia gas was passed into a stirred solution of 7.7 g. of methyl 2-[(N-chloroacetyl-N-methyl)amino]benzoate in 500 ml. of methanol for 6 hr. The mixture was allowed to remain at room temperature for 12 hr. and was evaporated *in vacuo*. The residue was recrystallized from methylene chloride-ether, giving 3.2 g. (53%) of the product, m.p. 192-193°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.00; H, 5.07; N, 14.89.

4-Benzyl-1-methyl-3H-1,4-benzodiazepine-2,5(1H,4H)-dione (VIIb).

A solution of 24.1 g. (0.1 mole) of methyl 2-[(N-chloroacetyl-N-methyl)amino]benzoate and 60 ml. of benzylamine was heated for 24 hr. on a steam bath. The mixture was evaporated *in vacuo*, diluted with 150 ml. of water, and extracted with benzene. The extract was washed successively with 2N sodium hydroxide, 2N hydrochloric acid, water, and was dried over anhydrous sodium sulfate. After removal of the solvent, the residue was recrystallized from ethanol-petroleum ether (b.p. 60-68°); yield 21.0 g. (75%), m.p. 111-112°.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 10.00. Found: C, 72.74; H, 5.86; N, 10.00.

1,3-Dimethyl-2,4(1H,3H)-quinazolinedione (VIIIa). (10)

A mixture of 0.5 g. of 2-[(N-chloroacetyl-N-methyl)amino]-N-methylbenzamide and 7 ml. of pyridine was refluxed for 1 hr. The mixture was evaporated *in vacuo* and the residue was triturated with water, and recrystallized from ethanol; m.p. 164-165°; yield, 0.2 g. (50%).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.34; H, 5.48; N, 14.69.

1-Methyl-3-phenyl-2,4(1H,3H)-quinazolinedione (VIIIb).

A mixture of 1.5 g. of 2-[(N-chloroacetyl-N-methyl)amino]benzanilide and 10 ml. of pyridine was refluxed for 2.5 hr. After removal of the solvent, the residue was triturated with water, and recrystallized from ethanol; m.p. 229-230°; yield, 0.7 g. (56%).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.79; N, 11.11. Found: C, 71.22; H, 4.80; N, 11.17.

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REFERENCES

(1) S. Gärtner, *Ann.*, 322, 226 (1904).

(2) S. Archer, T. R. Lewis, M. J. Unser, J. O. Hoppe and H. Lape, *J. Am. Chem. Soc.*, 79, 5783 (1957).

(3) L. R. Hines, *Cur. Ther. Res.*, 2, 6 (1960).

(4) (a) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, 26,1111 (1961); (b) S. C. Bell, T. S. Sulkowski, C. Gochman and S. J. Childress, *ibid.*, 27, 562 (1962); (c) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy and A. Stempel, *ibid.*, 27, 3788 (1962); (d) S. C. Bell, C. Gochman and S. J. Childress, *J. Med. Pharm. Chem.*, 5, 63 (1962); (e) L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach and N. Steiger, *J. Med. Pharm. Chem.*, 6, 261 (1963); (f) L. H. Sternbach, E. Reeder, A. Stempel and A. I. Rachlin, *J. Org. Chem.*, 29, 332 (1964).

(5) M. Uskoković, J. Iacobelli and W. Wenner, *ibid.*, 27, 3606 (1962).

(6) 4-Chloro-N-methylisatoic anhydride, m.p. 218-219°, was prepared by heating 4-chloro-2-(methylamino)benzoic acid with ethyl chloroformate and acetyl chloride; see I. M. Heilbron, F. N. Kitchen, E. B. Parkes and G. D. Sutton, *J. Chem. Soc.*, 2167 (1925). N-Methylisatoic anhydride and 5-chloro-N-methylisatoic anhydride were kindly supplied by Maumee Chemical Co., Toledo, Ohio.

(7) D. J. Fry, J. D. Kendall and A. J. Morgan, *J. Chem. Soc.*, 5062 (1960).

(8) R. P. Staiger and E. B. Miller, *J. Org. Chem.*, 24, 1214 (1959).

(9) Melting points were determined on Fisher-Johns block with calibrated thermometer.

(10) The infrared spectrum of VIIIa is identical with that reported in the literature; see H. Culbertson, J. C. Decius and B. E. Christensen, *J. Am. Chem. Soc.*, 74, 4834 (1952).

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