Studies on Meso-ionic Compounds. XIV[1]. Synthesis of Meso-ionic Compounds from Pyridazine Derivatives Having a Carboxymethylmercapto Group

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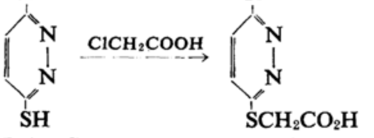
(Received April 3, 1961)

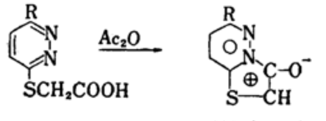
In the previous paper of this series, the reaction of several kinds of azoles (5-phenyl-1, 3, 4-triazole, 5-phenyl-1, 3, 4-oxadiazole, 1, 5-diphenyl-1, 3, 4-triazole, benzothiazole, benzoxazole, cyclohexeno- and cyclopentenothiazoles) having a carboxymethylmercapto group with acetic anhydride was reported[2]. Although no formation of pigments had been reported by Duffin et al.[3], it was demonstrated that not only the corresponding meso-ionic compounds but also pigments are formed in the reaction.

In this paper, the present authors further extended this reaction to pyridazine derivatives and studied whether the meso-ionic compounds are obtained or not from the pyridazine derivatives possessing a carboxymethylmercapto group by the loss of one mole of water. The structure of the resulting meso-ionic compounds from pyridazine derivatives was confirmed by infrared absorption, hydrolysis, and the reaction of the compounds with phenylhydrazine or mercuric chloride.



I (a—f) II (a—f)

a: $R=CH_3$
b: $R=SCH_3$
c: $R=SCH_2Ph$
d: $R=Cl$
e: $R=Ph$
f: $R=SH$



II (a—e) III (a—e)

Pyridazine derivatives possessing a carboxymethylmercapto group[4] were prepared from the corresponding mercapto pyridazine derivatives by the reaction with monochloroacetic acid. By the action of acetic anhydride or acetic anhydride-pyridine on 3-methyl-6-(carboxymethylmercapto)-pyridazine (IIa), violet pigment, which was not prosecuted for detailed investigation because of its difficult purification, was formed, and no corresponding meso-ionic compound was formed. But the present authors have found that IIa reacts readily with acetic anhydride-pyridine-triethyl amine to give a red meso-ionic compound IIIa by the loss of one mole of water, and in the same manner as in the case of IIa the other meso-ionic compounds IIIa—IIIe are obtained from those corresponding parent acids IIa—IIe, respectively. Unlike those reported previously[2], however, the present compounds are not formed in the absence of triethylamine as a more basic tertiary base, and by moisture in the air or in the solvent of recrystallization the new red compounds IIIa—IIIe immediately are turned into pale yellow compounds of which analytical values show their structures to be meso-ionic compounds IIIa—IIIe having a water of crystallization and which reversibly return to the red compounds of IIIa—IIIe on drying. These meso-ionic compounds are heat-unstable solids which are readily soluble in polar and non-polar solvents. For example, meso-ionic compounds give yellow aqueous solutions with the exception of IIIe and red solution in absolute ethanol or dry benzene. The influence of the substituent in 3-position of pyridazine on the ring closure of II by acetic anhydride was scarecely observed. Only 3-mercapto-6-(carboxymethylmercapto)-pyridazine (IIf) gave no mese-ionic compound. On storage, IIIa deteriorated and became black after about two weeks at room temperature. Though the other compounds IIIb—IIIe are stable, IIIa—IIIe turn black in pyridine or 10% aqueous sodium hydroxide. The infrared spectra of IIIa—IIIe respectively, in comparison with those of the parent acids, have a new strong absorption at 1630~1650 cm^{-1} with the disappearance of a band near 1700 cm^{-1} due to carbonyl vibration of the carboxy group. This similar remarkable change of the spectra of meso-ionic compounds from these pyridazine derivatives has been observed also in infrared spectra of meso-ionic

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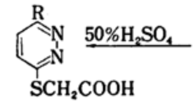
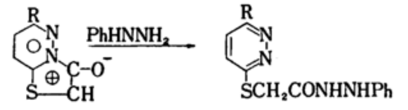
[1] Part XIII, This Bulletin, **34**, 668 (1961).
[2] M. Hashimoto and M. Ohta, ibid., **33**, 1394 (1960).
[3] G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, **1951**, 734; ibid., **1956**, 361.
[4] M. Kumagai, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **81**, 1604, 1886 (1960).

compounds derived from 2-(carboxymethylmercapto)-pyridine, whose structure had been confirmed synthetically[3], and from azoles having a carboxymethylmercapto group[2]. By 50% aqueous sulfuric acid IIIa—IIIe were easily hydrolyzed to the corresponding parent acids IIa—IIe respectively. The meso-ionic compounds IIIa, IIIb and IIIe reacted with mercuric chloride in methanol respectively to give pale yellow precipitates, whose analytical values suggest the structures to be IIIa + $2HgCl_2$, IIIb + HgCl and IIIe + HgCl respectively[5,6], but in the case of the parent acids IIa—IIe no such precipitates were formed. When meso-ionic compounds IIIa, IIIb and IIIe were heated with phenyl hydrazine in ethanol, the corresponding phenylhydrazides (IVa, IVb and IVe) were obtained. The fact that the corresponding phenylhydrazones were not formed, suggests that the C–O bond of the meso-ionic compounds has no ketonic character.



II (a—e)



III IV(a, b and e)

Experimental

3-Benzylmercapto-6-mercaptopyridazine.—A solution of benzylchloride (0.8 g.) in methanol (2 ml.) was poured into a solution of 3,6-dimercaptopyridazine[4] (0.8 g.) and sodium hydroxide (0.2 g.) in methanol (14 ml.). The solution was heated at 70°C on a water bath for 5 min., and 10% aqueous sodium hydroxide was added. The insoluble substance was filtered off. The filtrate was neutralized with aqueous hydrochloric acid to precipitate 3-benzylmercapto-6-mercaptopyridazine. Recrystallization from glacial acetic acid gave pale yellow needles (0.9 g.), m. p. 178~179°C. Yield 68.7%.

Found: N, 11.90. Calcd. for $C_{11}H_{10}N_2S_2$: N, 11.96%.

The alkali insoluble substance described above was recrystallized from ethanol to give white needles of 3,6-bis(benzylmercapto)-pyridazine, m. p. 121~122°C.

Found: N, 8.74. Calcd. for $C_{18}H_{16}N_2S_2$: N, 8.64%.

3-Methyl-6-(carboxymethylmercapto)-pyridazine (Ia).—A solution of chloroacetic acid (3.75 g.) and sodium hydroxide (1.6 g.) in water (16 ml.) was

TABLE I. 3-SUBSTITUTED PYRIDAZINE DERIVATIVES HAVING A CARBOXYMETHYLMERCAPTO GROUP IN THE 6-POSITION

	R	Appearance	M. p., °C	Yield, %	Formula	Anal. N% Found	(Calcd.)
IIb	SCH_3	White plates	183~184	78.3	$C_7H_8O_2N_2S_2$	13.04	(12.96)
IIc	SCH_2Ph	White plates	108~109	72.5	$C_{13}H_{13}O_2N_2S_2$	9.67	(9.59)
IId	Cl	7)					
IIe	Ph	White plates	149~150	theor.	$C_{12}H_{10}O_2S$	11.60	(11.38)
IIf	SH	Yellow prisms	180 (decomp.)	71.4	$C_6H_6O_2N_2S_2$	13.56	(13.86)

TABLE II. MESO-IONIC COMPOUNDS FROM ACIDS IIb—IIe

	M. p., °C	Yield, %	Formula	Anal. C% Found (Calcd.)	H% Found (Calcd.)	N% Found (Calcd.)
IIIb	> 300	theor.	$C_7H_6ON_2S_2$	42.20 (42.43)	3.14 (3.05)	14.20 (14.14)
IIIc	167~168	81.8	$C_{13}H_{10}ON_2S_2$	57.07 (56.93)	3.89 (3.68)	10.19 (10.22)
IIId	> 250	80.0	$C_6H_3ON_2SCl$	38.30 (38.57)	1.96 (1.61)	14.87 (11.38)
IIIe	110 (decomp.)	(60.0)	$C_{12}H_{10}O_2N_2S$ (having H_2O)	60.43 (58.53)	4.38 (4.09)	11.38 (11.38)
	122 (decomp.)	60.0	$C_{12}H_8ON_2S$	62.78 (63.16)	3.55 (3.53)	12.13 (12.28)

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5) G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, **1956**, 3189.

6) H. Kato et al., *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippan Kagaku Zasshi*), **78**, 707 (1957).

7) J. Kinugawa et al., *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **80**, 1559 (1960).

added to a solution of 3-methyl-6-mercapto-pyridazine (5.0 g.)[4] and sodium hydroxide (1.6 g.) in water (16 ml.). The solution was warmed on a water bath at 60∼65°C for an hour. After cooling, the reaction mixture was neutralized with 10% aqueous hydrochloric acid and the resulting precipitate was filtered off. Recrystallization from ethanol gave white plates (4.3 g.) m. p. 138∼139°C. Yield 58.9%.

Found: C, 45.50; H, 4.52; N, 14.90. Calcd. for $C_7H_8O_2N_2S$: C, 45.65; H, 4.34; N, 15.22%.

IIb, IIc, IId, IIe and IIf[4]. — These acids were prepared by the same procedure as used for Ia. The following Table I set forth these results.

Meso-ionic Compound IIIa from IIa.—The acid IIa (4.0 g.) was dissolved at room temperature in a mixture of acetic anhydride, pyridine and triethylamine (volume ratio of 1 : 1 : 1) (5 ml.). The solution immediately turned red and after a few minutes orange crystals were separated, which were filtered off, and completely washed with ether. Recrystallization from ethanol-ligroin gave pale yellow needles, m. p. 106°C (decomp.), which have a water of crystallization.

Found: C, 45.60; H, 4.45; N, 15.14. Calcd. for $C_7H_6ON_2S\cdot H_2O$: C, 45.65; H, 4.38; N, 15.21%.

When this compound was heated at about 65°C under reduced pressure, the water of crystallization was removed, affording red crystals of IIa, m. p. 135°C (decomp.). Yield 2.0 g. (50.0%).

Found: C, 50.30; H, 3.72; N, 16.54. Calcd. for $C_7H_6ON_2S$: C, 50.60; H, 3.64; N, 16.87%.

Meso-ionic Compound IIIb, IIIc, IIId and IIIe Derived from Acids IIb, IIc, IId and IIe Respectively.—In exactly the same manner as in the case of IIa, these meso-ionic compounds were obtained from the corresponding parent acids IIb, IIc, IId and IIe respectively, and are listed in Table II.

Action of Aqueous Sulfuric Acid on IIIa.—A suspension of IIIa (0.3 g.) in 50% aqueous sulfuric acid (1 ml.) was refluxed gently for 5 min. The solution slowly turned red to yellow. After cooling, the solution was neutralized with 10% aqueous sodium hydroxide and was concentrated under diminished pressure. Absolute ethanol (50 ml.) was added to the concentrated solution and the resulting precipitate was filtered off. Crude crystals obtained by concentration of the filtrate were recrystallized twice from ethanol, to afford white plates (0.15 g.), m. p. 139°C, which were undepressed by admixture with an authentic sample of IIa.

Action of Aqueous Sulfuric Acid on IIIb and IIIe.—The reaction product, from IIIb or IIIe by a method similar to that for IIa, was undepressed by the admixture with authentic sample of IIb or IIe. Yield of IIb, 81.7% and that of IIe 40%.

Action of Aqueous Sulfuric Acid on IIIc. — A suspension of IIIc (0.1 g.) with 50% aqueous sulfuric acid (2 ml.) was gently boiled for 10 min., and after cooling, the solution was neutralized with 10% aqueous sodium hydroxide and was extracted with ether. The extract was dried over anhydrous sodium sulfate and was evaporated to dryness. The residue was recrystallized from glacial acetic acid affording 0.07 g. of white plates m. p. 108∼109°C, which showed no depression on admixture with an authentic specimen of IIc.

Action of Aqueous Sulfuric Acid on IIId. — In the same manner as in the case of IIIc, the parent acid IIc was obtained.

Reaction of IIIa, IIIb and IIIe Respectively, with Mercuric Chloride[5,6]. — The solution of IIIa (0.7 g.) and sodium acetate (0.7 g.) in 50% aqueous methanol (20 ml.) was added to a solution of mercuric chloride (1.1 g.) in 50% aqueous methanol (5 ml.). The solution immediately turned yellow to separate a yellow precipitate (1.3 g.). Recrystallization from ethanol gave pale yellow crystals, m. p. > 230°C.

Found: N, 4.22. Calcd. for $C_7H_6ON_2SHg_2Cl_4$: N, 3.94%.

Yellow precipitate from IIIb or IIIe was prepared by the same method as used for IIIa and yellow precipitate from IIIb has m. p. > 300°C.

Found: N, 6.71. Calcd. for $C_7H_5ON_2S_2HgCl$: N, 6.47%. M. p. 250°C (decomp.) from IIIe, Found: N, 5.73, 5.71. Calcd. for $C_{12}H_7ON_2SHgCl$: N, 6.05%.

Action of Phenylhydrazine on IIIa.—A solution of phenylhydrazine (0.1 g.) in absolute ethanol (1 ml.) was added to a solution of IIIa (0.1 g.) in absolute ethanol (2 ml.) and the solution was refluxed on a water bath for 15 min. and decolorized with charcoal. The residual oil obtained by evaporation of alcohol solidified giving crude crystals (0.1 g.), m. p. 125∼126°C, on cooling in an ice bath for 1 hr. Twice recrystallization from ethanol-ligroin yielded a pure sample of the corresponding phenylhydrazide (IVa) as orange needles, m. p. 138∼139°C.

Found: C, 56.43; H, 5.21; N, 20.32, 20.24. Calcd. for $C_{13}H_{14}ON_4S$: C, 56.92; H, 5.15; N, 20.43%.

Action of Phenylhydrazine on IIIb and IIIe.—In exactly the same manner as described above, phenylhydrazides (IVb and IV) were prepared, IVe was plates (33.9%), m. p. 181∼181.5°C.

Found: C, 64.14; H, 4.93; N, 16.42. Calcd. for $C_{18}H_{16}ON_4S$: C, 64.27; H, 4.80; N, 16.66%. IV, m. p. 152∼153°C. Found: N, 18.75. Calcd. for $C_{13}H_{14}ON_4S_2$: N, 18.29%.

The authors are indebted to Dr. Asaji Kondo for microanalyses.

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