low needle-like crystals, m.p. 185–188° (reported 191° dec.[2]).

p-Nitrophenylsemicarbazide hydrochloride. This compound was prepared by dissolving 2 g. of *p*-nitrophenylsemicarbazide in 100 ml. of boiling absolute ethanol and adding 1 ml. of concentrated hydrochloric acid. Crystalline product in quantitative yield was obtained on cooling, m.p. 239° dec. (reported 265° dec.[2]).

p-Nitrophenylsemicarbazones. The general procedure for the preparation is described here. A saturated solution of *p*-nitrophenylsemicarbazide hydrochloride in 0.1*N* hydrochloric acid containing 1 or 2 millimole of the reagent was mixed with 1 millimole of the carbonyl compound dissolved in minimal amount of water or 0.1*N* hydrochloric acid. The precipitate thus obtained was collected on a glass funnel and washed with water. The crude product was dried and purified by recrystallization from ethanol, 50% ethanol, glacial acetic acid, or 50% acetic acid as indicated in Table I.

TABLE I

p-NITROPHENYLSEMICARBAZONES R=N—NH—C_6H_4—NO_2

	R	Yield, %	M.P.	Solvent for Recrystallization
1.	CH_3CH=	62	200° dec.	Ethanol
2.	$(CH_2OH)_2C$=	62	192° dec.	Ethanol
3.	CH_2OH—CHOH—CH=	52	196° dec.	Ethanol
4.	CH_3C= HC=	20	246° dec.	Acetic acid
5.	C_2H_5C= COOH	57	205° dec.	Acetic acid
6.	HOOC$(CH_2)_2C$= COOH	85	181° dec.	50% Ethanol
7.	(C_2H_5)OOCCH_2C= CH_3	69	174–175°	Ethanol
8.	HOOCCH_2C= COOH	65	219° dec.	50% Acetic acid
9.	HOOCC= HOOCCH HOOCCH_2	7	150° dec.	Acetic acid
10.	HOOCC= $CH_2.C_6H_5$	66	197° dec.	Acetic acid

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DEPARTMENT OF PEDIATRICS AND COMMUNICABLE DISEASES
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Isolation of Two Sodium Methazonates

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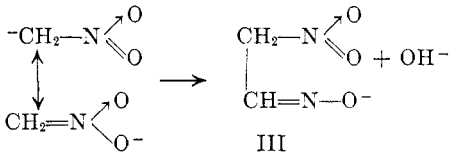
Methazonic acid is usually prepared by the action of concentrated sodium hydroxide solution on nitromethane.[1]

Various attempts have been made to formulate a mechanism for the reaction but with little success. Levy and Rose[2] stated that an intermediate monosodium compound I is formed by the interaction of nitromethane and its sodium salt. This is then dehydrated to form monosodium methazonate II.

$$O_2N—CH_2—CH_2—N(OH)—ONa \longrightarrow$$
I

$$HO—N=CH—CH=NO_2Na$$
II

Drew, McNesby, and Gordon,[3] however, who studied the reaction spectrophotometrically, stated that the methazonate anion III is formed by the reaction of two nitromethane anions, although the structure III would involve the formation of hydroxyl ions in a strongly alkaline medium.



III

The work reported in this paper shows that the reaction product is a disodium salt IV which is probably monohydrated. This then forms a hexahydrate which can be readily isolated from the solution.

TABLE II

p-NITROPHENYLSEMICARBAZONES R=N—NH—C_6H_4—NO_2

	Analysis							
	Carbon, %		Hydrogen, %		Nitrogen, %			
R	Calcd.	Found	Calcd.	Found	Calcd.	Found	λ_{max}	ϵ
1.	48.65	48.69	4.54	4.89	25.22	25.55	322	186,000
2.	44.77	44.64	4.51	4.25	20.89	20.76	322	213,000
3.	44.77	45.01	4.51	4.35	20.89	20.21	323	183,000
4.	47.66	47.30	3.77	3.81	26.16	26.86	331[a]	640,000[a]
5.	47.14	47.06	4.32	4.25	19.99	19.40	319	228,000
6.	40.00[b]	40.02	4.48[b]	4.40	15.55[b]	15.66	317	201,000
7.	50.65	50.83	5.23	5.65	18.18	17.94	322	197,000
8.	42.59	42.90	3.25	3.54	18.06	18.02	318	216,000
9.	42.40	42.96	3.29	3.42	15.22	15.09	319	208,000
10.	56.14	55.96	4.12	4.15	16.37	16.22	318	216,000

[a] In glacial acetic acid. [b] On basis of two moles of water of crystallization.

$$^-O—N=CH—CH=NO_2^-$$
IV

The formation of a disodium salt supports Drew's

(1) W. Meister, *Ber.*, **40**, 3435 (1907).
(2) N. Levy and J. D. Rose, *Quart. Revs.* (*London*), **1**, 358 (1947).
(3) C. M. Drew, J. R. McNesby, and A. S. Gordon, *J. Am. Chem. Soc.*, **77**, 2622 (1955).

proposed mechanism and is more acceptable on theoretical grounds than the formation of the monosodium salt III since it does not require the elimination of hydroxyl ion.

EXPERIMENTAL

Sodium methazonate was prepared using part of the procedure described by Meister[1] for the preparation of the acid. Nitromethane (8.5 ml.) was run in small portions into a cold stirred solution of 10 g. sodium hydroxide in 20 ml. water. The temperature of the solution was not allowed to exceed 40°. White crystals of the sodium derivative were formed; these dissolved slowly and the solution became first yellow and then deep cherry red. When the solid had completely dissolved, the solution was warmed for a few minutes at 50–55°.

At this stage, the methazonic acid is normally liberated by acidification but to obtain the intermediate sodium salt, the solution was cooled to 5–10° when it became viscous and solidified more or less completely. Absolute alcohol was added to aid filtration and the cream colored solid filtered off. This was decolorized further by solution in a minimum of water followed by precipitation with ice-cold alcohol. An almost white solid was obtained; this was dried with alcohol and ether.

RESULTS AND DISCUSSION

Titration of the sodium salt. Potentiometric titration of a solution of the sodium salt with 0.1N hydrochloric acid gave a titration curve (Fig. 1a) with a sharp change in *p*H around 9.5 and

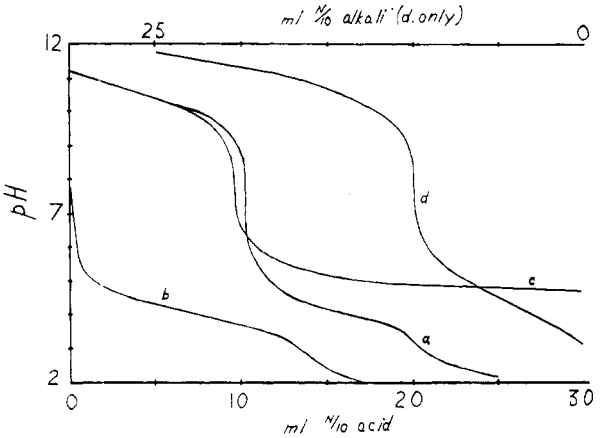


Fig. 1. Titration curves. *a.* Disodium methazonate. *b.* Monosodium methazonate. *c.* Disodium methazonate-acetic acid. *d.* Methazonic acid.

an inflection at *p*H × 3. The end point at *p*H 9.5 corresponded to an equivalent weight of about 260: monosodium methazonate has an equivalent weight of 126.

In view of this, similar titrations were carried out on a number of different preparations but an equivalent in the range 258–261 and a second point of inflection at *p*H 3 were always obtained. The titration curve is reversible when the liberated acid is back titrated without much delay.

Analysis of the sodium salt. Combustion analysis was impractical as the sodium salt deflagrated on heating. Determination of nitrogen by a modified Kjeldahl method and of sodium by flame photometry gave the following results.

N 10.7%; Na 18.8%

Loss in weight of the sodium salt. When the sodium salt was dried *in vacuo* over P_2O_5, a very hygroscopic pale yellow solid was obtained. The loss in weight was 35.9%.

These results correspond to a hydrated disodium salt. The hexahydrate corresponding to IV has the following composition.

Equiv. weight 256; N 10.8%; Na 18.0%

A loss in weight on drying of 35.9% corresponds to the loss of only 5 molecules of water of crystallization (theoretical 35.2%). The vacuum-dried material was analyzed. The results below are compared with those calculated for a monohydrate.

Calculated: equiv. wt. 166; N 16.9%; Na 27.7%
Found: equiv. wt. 172; N 16.2%; Na 28.0%

That the dried solid still contains water of crystallization was confirmed by infrared analysis. The final molecule of water is thus very tenaciously held, which suggests that a monohydrate is formed as the primary product of the reaction.

Isolation of monosodium methazonate. The cold cherry-red solution obtained in the above preparation was titrated with 10*N* hydrochloric acid to *p*H × 4.3, the temperature being maintained below 10°. A yellowish white solid crystallized out. This was filtered off, washed with a minimum of alcohol, and again precipitated from concentrated aqueous solution with ice-cold alcohol. It did not lose weight on keeping *in vacuo* over P_2O_5; its analysis gave the following results, which are compared with values calculated for monosodium methazonate II.

Calculated: equiv. wt. 126; N 22.2%; Na 18.2%
Found: equiv. wt. 129; N 21.2%; Na 18.1%

The titration curve (Fig. 1b) was almost identical with the second part of that of the disodium salt.

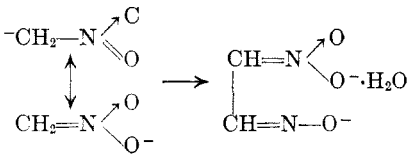
Methazonic acid. The point of inflection at *p*H 3 of the sodium methazonate titration corresponds to the titration of the nitroxylate ion $=N\begin{matrix}O\\ \nearrow\\ \searrow\\ O^-\end{matrix}$ so that the product of acidification is the aci-nitro form. This is unstable but a strong acid; as would be expected, the titration curve with acetic acid (Fig. 1c) does not show the second point of inflection. The instability of the aci-form would account for the formation of a red oil which always occurs in the preparation of the acid by this method.

The reversibility of the titration indicates that the aci-nitro group can be back-titrated with alkali if this is done without isolating the acid. When a prepared specimen of methazonic acid was

titrated potentiometrically with 0.1*N* sodium hydroxide however, the titration curve (Fig. 1d) showed only one sharp change in *p*H (corresponding to an equivalent of 104) and no other point of inflection.

Methazonic acid therefore normally functions as a monobasic acid $O_2NCH_2CH{=}NO^-H^+$ but in its preparation from nitro methane, an intermediate disodium salt is formed.

Bearing in mind that Drew's kinetic studies showed that the reaction involved two univalent negative ions, a more correct representation of its formation is therefore



although an intermediate compound could well be formed.

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Reaction of 1-Chloroisoquinoline with Peracetic Acid[1]

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As part of an investigation[2,3] of the rearrangement of isoquinoline-*N*-oxides, attempts were made to prepare 1-chloroisoquinoline-*N*-oxide by the reaction of 1-chloroisoquinoline with aqueous peracetic acid. Oxidations of this type have been effected with 2-bromopyridine using 40% peracetic acid[4] and with other α-halo-heterocycles. The desired oxide was not obtained, for the reaction took another course, but since several new isoquinoline derivatives were prepared, and since certain of the transformations were unexpected, the results are reported here.

When 1-chloroisoquinoline[5] was heated with acetic acid and hydrogen peroxide at 65°, a substance with the anticipated composition was obtained in consistently low yield, along with much colored, polymeric material. On treatment of the purified product with acetic anhydride, an acetyl derivative was formed, which, however, reverted to the starting material on hydrolysis. The oxidation product was eventually shown to be 4-chloroisocarbostyril by hydrogenolysis to isocarbostyril and by conversion to the known[5] 1,4-dichloroisoquinoline. Further, 1,4-dichloroisoquinoline, which may be prepared more conveniently by the action of phosphorus pentachloride on isocarbostyril[6] than by the method of Gabriel and Colman, was converted to 4-chloroisocarbostyril by methanolysis of the 1-chloro group and subsequent cleavage of the ether with hydrochloric acid.

It was found that the mode of formation of the unexpected product involved a surprisingly facile hydrolysis of the 1-chloroisoquinoline, followed by chlorination of the resulting isocarbostyril by the free halogen formed from the chloride ion liberated in the oxidizing medium. Although acid-catalyzed nucleophilic substitutions with 1-chloroisoquinoline are well known,[7] the conditions of the attempted oxidation are unusually mild for such a hydrolysis. Convincing evidence was obtained for this reaction course, however: 1. Treatment of 1-chloroisoquinoline with acetic acid and water under conditions identical with those of the oxidation resulted in the formation of a 38% yield of isocarbostyril and the recovery of 52% of the starting material. 2. Treatment of isocarbostyril with a mixture of hydrogen peroxide, hydrochloric acid, and glacial acetic acid produced 4-chloroisocarbostyril rapidly in 87% yield. 3. Prolonged treatment of 1-chloroisoquinoline with acetic acid and water at the reaction temperature before addition of the hydrogen peroxide resulted in an increased yield of 4-chloroisocarbostyril. 4. Addition of bromide ion to a 1-chloroisoquinoline-oxidation mixture resulted in the formation of 4-bromoisocarbostyril.

EXPERIMENTAL[8,9]

4-Chloroisocarbostyril. A mixture of 1.64 g. of 1-chloroisoquinoline,[5] 1 ml. of 30% hydrogen peroxide, and 3 ml. of glacial acetic acid was heated at 65° for a period of 12 hr., 0.8 ml. more hydrogen peroxide being added after 3 hr. The reddish solution, from which crystals separated during the

(1) This investigation was supported in part by a research grant, number C-2574, from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) M. M. Robison and B. L. Robison, *J. Org. Chem.*, **21**, 1337 (1956).

(3) M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.*, in press.

(4) E. Shaw, J. Bernstein, K. Losee, and W. A. Lott, *J. Am. Chem. Soc.*, **72**, 4362 (1950).

(5) S. Gabriel and J. Colman, *Ber.*, **33**, 980 (1900).

(6) Cf. S. Gabriel, *Ber.*, **18**, 3470 (1885) for the corresponding reaction with 3-phenylisocarbostyril.

(7) Cf. W. J. Gensler in *Heterocyclic Compounds*, R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, N. Y., 1952, Vol. 4, p. 421.

(8) Melting points are corrected.

(9) Analyses by Weiler and Strauss, Oxford, England, and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., except for some nitrogen analyses which were carried out by a semimicro Kjeldahl technique in this laboratory.