supernatant of the ammonolysis mixture gave a 50% yield of ethyl carbamate on work-up. Equation 1 is a rationalization of the reaction sequence.

At first glance the driving force for the reaction would seem to be the release of steric strain to give a resonance-stabilized product. However, construction of molecular models[8] indicates that a planar configuration of the propenide ion is subject to a much larger degree of steric crowding than is the cyclopropane. Even if the carbon-carbon bonds of the propane molecules are allowed to rotate freely, thus destroying allylic resonance, the most favorable conformation is not improved over the cyclopropane with respect to steric crowding. An acceptable rationale for the reaction is not evident.

Experimental

Diethyl 1,1-Dicyanoethylene-2,2-dicarboxylate (III).—Malonitrile (6.6 g., 0.10 mole) was dissolved in diethyl ketomalonate (17.4 g., 0.10 mole, Pierce Chemical Co.) contained a flask protected from moisture and cooled in an ice bath. One drop of base catalyst ($^2/_3$ dioxane, $^1/_3$ piperidine) was added. At the end of 3 hr. the contents had become a solid waxy white mass. Filtration under nitrogen gave a white hygroscopic residue and a yellow oily filtrate.

The white solid was shown to be diethyl dihydroxymalonate by comparison (infrared) with an authentic specimen.

The yellow oil was fractionated through a spinning brush column: 1.2 g., b.p. 60–97° (1.5 mm.) and 13.1 g., b.p. 97–99° (1.5 mm.). The 97–99° fraction was redistilled through the spinning brush column: 11.7 g., b.p. 86.0° (1.0 mm.) collected in six fractions, $n^{24}\text{D} = 1.4620–1.4628$. The center fraction, $n^{24}\text{D}$ 1.4628, was analyzed.

Anal. Calcd. for $C_{10}H_{10}N_2O_n$: C, 54.0; H, 4.5; N, 12.6; mol. wt., 222. Found: C, 54.23, 54.25; H, 4.56, 4.95; N, 12.80, 12.67; mol. wt., 203, 205.

The NMR spectrum (40 mc./sec.) shows only O—CH_2—CH_3 absorption. The infrared spectrum has a weak nitrile band at 2230 cm.$^{-1}$ (4.48 μ), a strong carbonyl at 1750 cm.$^{-1}$ (5.72 μ), and —C═C— at 1600 cm.$^{-1}$ (6.22 μ). The compound reduces permanganate readily but does not decolorize bromine in carbon tetrachloride, even on boiling. Its solution in benzene is colorless, but addition of anthracene gives a red-brown complex. An equimolar mixture of the compound and anthracene is red-brown, but after heating to 150° and cooling, a white adduct forms. Crystallization from ethanol–water, then from cyclohexane gave white crystals, m.p. 153.6–155.2°.

Anal. Calcd. for $C_{24}H_{20}N_2O_4$: C, 72.0; H, 5.0; N, 7.0. Found: C, 72.16, 71.84; H, 5.13, 5.19; N, 6.96, 6.94.

The adduct is thermochromic, turning red-brown on melting and white again on resolidifying.

Diethyl 1,1,2,2-Tetracyanocyclopropane-3,3-dicarboxylate (I).—To the product resulting from the reaction of malonitrile (38 g., 0.575 mole) and diethyl ketomalonate (100 g., 0.575 mole) (this time a yellow viscous fluid), ethanol (250 ml., commercial absolute) was added and the mixture stirred to effect solution. While cooling the mixture in an ice bath, bromine (52 g., 0.28 mole) was added dropwise slowly. The resulting dark red-brown solution was poured onto 1 kg. of ice to give a yellow oil, which crystallized on being stirred overnight. The precipitate was washed with water, then dried over phosphorus pentoxide under vacuum to give 71.5 g. (0.25 mole, 87%) of product, m.p. 129.4–130.8°. A sample crystallized from ethanol–water, carbon tetrachloride, and then hexane was sublimed at 1 mm. pressure and 110° to give white crystals, m.p. 129.6–131.2°.

Anal. Calcd. for $C_{13}H_{10}N_4O_4$: C, 54.5; H, 3.5; N, 19.6; mol. wt., 286. Found: C, 54.80, 54.70; H, 3.81, 3.51; N, 19.44, 19.37; mol. wt., 297, 280.

The NMR spectrum (40 mc./sec.) shows only O—CH_2—CH_3 absorption. The infrared spectrum has only a barely perceptible nitrile band at 2240 cm.$^{-1}$ (4.46 μ), a strong CO at 1765 cm.$^{-1}$ (5.70 μ), and no absorption between 1765 (5.70 μ) and 1500 cm.$^{-1}$ (6.7 μ) (*i.e.*, no —C═C—).

Ammonium 1,1,3,3-Tetracyano-2-carbethoxypropenide (IV).—Diethyl 1,1,2,2-tetracyanocyclopropane-3,3-dicarboxylate (I) (15.0 g., 0.052 mole) was suspended in ether (500 ml., distilled from calcium hydride) in a flask protected from moisture. Dry ammonia (approx. 15 g.) was allowed to distill from a solution of sodium in ammonia and drop from a Dry Ice–acetone cooled condenser into the ethereal suspension of I. The first drops of ammonia gave a yellow oily precipitate which soon solidified to a brown cake. After stirring overnight, the mixture was filtered to give 11.4 g. of brown amorphous solid, m.p. 192–201° dec. The filtrate was evaporated to dryness and the pasty orange residue was stirred with chloroform, leaving a yellow chloroform solution and 0.5 g. of yellow powder, m.p. 203° (decompn.). Mixed m.p. of this latter yellow powder with the first precipitate was 197–204° (decompn.). The chloroform-insoluble material was washed with excess chloroform and dried *in vacuo.*

Anal. Calcd. for $C_{19}H_{13}N_5O_2$: C, 52.1; H, 4.3; N, 30.3. Found: C, 52.34; H, 4.21; N, 30.50.

The chloroform solution was decolorized with charcoal and evaporated to dryness to give white crystals, m.p. 46.6–48.6°, whose infrared spectrum was superimposable on that from an authentic specimen of ethyl carbamate.

The infrared spectrum of the orange solid has a very strong nitrile band at 2190 cm.$^{-1}$ (4.57 μ), a strong CO at 1730 cm.$^{-1}$ (5.78 μ), no absorption between 1730 (5.8 μ) and 16.50 cm.$^{-1}$ (6.5 μ), but a strong band at 1510 cm.$^{-1}$ (6.62 μ) assigned to the —C═C—.

Quinolinium-1,1,3,3-tetracyano-2-carbethoxypropenide.—To an aqueous solution of IV was added a concentrated aqueous solution of quinolinium hydrochloride. An immediate orange precipitate formed, several recrystallizations of which from water gave a product of m.p. 51–52°. Drying in high vacuum over phosphorus pentoxide at 60° gave a product of m.p. 111.5–112.5°.

Anal. Calcd. for $C_{19}H_{13}N_5O_2$: C, 66.5; H, 3.8; N, 20.4. Found: C, 66.79, 66.88; H, 3.77, 4.00; N, 20.03, 20.0.

Recrystallization of the 111.5–112.5° product from water gave a product of m.p. 51–52°, presumably a hydrate.

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[8] Godfrey Molecular Models, *J. Chem. Ed.*, **36**, 140 (1959).

S-Acylthiosemicarbazones

WILLIAM R. SHERMAN AND ARTHUR A. ALTER

Scientific Divisions Abbott Laboratories, North Chicago, Ill.

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While investigating methods for the preparation of 1-(5-nitro-2-furoyl)thiosemicarbazides,[1] a paper was found wherein the authors[2] treated *p*-nitrobenzoyl chloride and other acid chlorides with thiosemicarbazide in *acetone* to obtain 1-*p*-nitrobenzoyl and other 1-acylthiosemicarbazides. This reaction was verified in our laboratory. However, when 5-nitro-2-furoyl chloride was substituted for the nitrobenzoyl chloride, *S*-(5-nitro-2-furoyl)ace-

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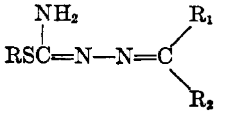
[1] W. R. Sherman, *J. Org. Chem.*, **26**, 88 (1961).

[2] M. Ohta and T. Higashijima, *J. Pharm. Soc. Japan.*, **72**, 376 (1952).

TABLE I

S-ACYLTHIOSEMICARBAZONES



R	R_1	R_2	Yield, %	M.P.[a]	Color	Crystallized from
5-Nitro-2-furoyl (I)	CH_3	CH_3	88	204 dec.	Deep red	D.M.F.[c]–H_2O
5-Nitro-2-furoyl (II)	C_2H_5	C_2H_5	36	186–187 dec.	Red	HOAc–H_2O
5-Nitro-2-furoyl (III)	CH_3	C_2H_5	51	190–191 dec.	Red	2-butanone
5-Nitro-2-furoyl (IV)	CH_3	CF_3	18	155–156 dec.	Red	T.H.F.[e]–$(C_2H_5)_2O$
5-Nitro-2-furoyl (V)	CH_3	$-\overline{CHCH_2CH_2}$	60	169–170 dec.	Orange-red	T.H.F.–C_6H_6
5-Nitro-2-furoyl (VI)	CH_3	$-CH_2CH_2COOH$	56	166–167 dec.	Red	T.H.F.–$(C_2H_5)_2O$
5-Nitro-2-furoyl (VII)	CH_3	C_6H_5	36	168–169 dec.	Orange-red	D.M.F.–H_2O
5-Nitro-2-furoyl (VIII)	$-CH_2CH_2CH_2CH_2-$		78	192–193 dec.	Red	T.H.F.
5-Nitro-2-furoyl (IX)	H	$-CH=CHC_6H_5$	87	207 dec.	Orange-red	D.M.F.–H_2O
2-Furoyl (X)	CH_3	CH_3	77	145–146	Pale yellow	C_6H_6
p-Nitrobenzoyl (XI)	CH_3	CH_3	55	165 dec.	Yellow	C_2H_5OH
p-Chlorobenzoyl (XII)	CH_3	CH_3	70	169–170 dec.	White	C_2H_5OH

[a] See ref. 6. [b] See ref. 3. [c] Dimethylformamide. [d] Nujol mull. [e] Tetrahydrofuran. [f] 3.5% $CHCl_3$ solution. [g] 1.2% $CHCl_3$ solution.

tone thiosemicarbazone (I) was obtained in 66% yield. This, and other *S*-acylthiosemicarbazones, could also be prepared by treating the appropriate thiosemicarbazone with the required acid chloride (Table I). It is not known why the nitrofuroyl chloride and the nitrobenzoyl chloride follow different courses in the first-described reaction.

The *S*-acyl structure proposed for these substances is supported principally by two facts: the formation of a benzylidene derivative and the infrared spectra[3] of appropriate members of the series.

When I is warmed with benzaldehyde, a compound is formed which has the correct elemental analysis for the benzylidene derivative and which has no major absorption below 3.45 μ (Nujol). Under acid conditions, this readily reverts to I, which has two absorptions in this region (Table I).

The infrared spectra of three *S*-acylacetone thiosemicarbazones which could be determined in solution [2-furoyl (X), *p*-nitrobenzoyl (XI) and *p*-chlorobenzoyl (XII); see Table I] all show two absorptions in the 3-μ region, both of which lie in the proper range[4] for a primary amine. *S*-Benzylacetonethiosemicarbazone[5] shows similar absorption [2.89 (m), 2.98 (m), 7% in chloroform].

Both *S*-(5-nitro-2-furoyl)- and *S*-*p*-nitrobenzoylacetone thiosemicarbazone are insoluble in cold or boiling 25% sodium hydroxide solution, suggesting the absence of —SH, which also supports the *S*-acyl structure.

All of these compounds are highly colored. In particular, the nitrofuryl derivatives are usually a brilliant red. Several of the substances appeared to exist in two different colored modifications. For instance, *S*-*p*-nitrobenzoylacetone thiosemicarbazone can be crystallized from benzene to give orange needles and from ethanol to give a yellow form. Both of these forms have the same melting point and are identical in the infrared, both in Nujol mull and chloroform solution.

The most interesting of this series from a chemotherapeutic standpoint is *S*-(5-nitro-2-furoyl)-acetone thiosemicarbazone (I). This compound was found to protect up to 80% of mice which had been infected with a fatal *Trypanosoma cruzi* parasitemia, when given intraperitoneally, over a fifteen-day period, at a level of 33 mg./kg./day.

Experimental[6]

S-Acylthiosemicarbazones.—These compounds, whose properties are described in Table I, were prepared in dry tetrahydrofuran, with the exception of I, X, XI, and XII, where dry acetone was the reaction solvent.

In general, a solution of the appropriate thiosemicarbazone in the proper solvent was stirred at room temperature with 1.4 equivalents of sodium bicarbonate. To this was added a solution, in the same solvent, containing an equimolar quantity of the required acid chloride. After stirring for 2 hr., the reaction mixture was heated under reflux for 30 min., cooled, and filtered. The filter cake was washed with water and the product recrystallized from the proper solvent (Table I).

Occasionally, a quantity of 1-acylthiosemicarbazide could be isolated from these reactions as a minor by-product. Whether this arose by solvolysis of thiosemicarbazone or by thiosemicarbazide present in the starting material is not known, although the latter does not seem likely.

S-(5-Nitro-2-furoyl)acetone Thiosemicarbazone (I).—In

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(3) Infrared spectra were determined by W. Washburn of Abbott Laboratories whose aid in the interpretation of these data is acknowledged. Spectra were measured on a Perkin-Elmer Model 21 spectrophotometer.

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., Methuen and Co., Ltd., London, 1959, p. 249.

(5) F. J. Wilson and R. Burns, *J. Chem. Soc.*, **121**, 873 (1922).

(6) All melting points are uncorrected and were determined in capillary tubes. Analyses were carried out at Abbott Laboratories by E. F. Shelberg and his staff.

TABLE I (*Continued*)

Calcd.	Found	Calcd.	Found	Calcd.	Found	Infrared,[b] μ
N, 20.74	N, 20.68	O, 23.69	O, 23.97	S, 11.84	S, 11.91	3.06 (m), 3.18 (m)[d]
C, 44.29	C, 44.47	H, 4.73	H, 4.52	N, 18.78	N, 18.61	...
C, 42.25	C, 42.50	H, 4.26	H, 4.16	N, 19.71	N, 19.91	...
C, 33.34	C, 33.48	H, 2.18	H, 2.33	N, 17.28	N, 17.15	...
C, 44.59	C, 44.77	H, 4.08	H, 3.97	N, 18.91	N, 18.63	...
C, 40.24	C, 40.38	H, 3.68	H, 3.73	N, 17.07	N, 16.82	...
C, 50.59	C, 50.61	H, 3.64	H, 3.89	N, 16.86	N, 16.80	...
C, 44.59	C, 44.85	H, 4.08	H, 4.23	N, 18.91	N, 18.64	...
C, 52.31	C, 52.32	H, 3.51	H, 3.35	N, 16.28	N, 16.32	...
C, 47.98	C, 48.16	H, 4.92	H, 5.19	N, 18.65	N, 18.63	2.86 (m), 2.94 (m)[f]
C, 47.14	C, 47.16	H, 4.32	H, 4.49	N, 19.99	N, 19.80	2.86 (m), 2.94 (m)[f]
C, 48.98	C, 48.73	H, 4.49	H, 4.59	N, 15.58	N, 15.82	2.87 (m), 2.95 (m)[g]

addition to the general procedure described above, this may be prepared in the following way. To a solution of 5.27 g. (0.03 mole) of 5-nitro-2-furoyl chloride in 100 ml. of cold acetone was added, in the following order, 2.73 g. (0.03 mole) of thiosemicarbazide and 7 g. of sodium bicarbonate. After stirring for 3 hr., the suspension was heated under reflux for 1 hr., cooled, and filtered. The filtrate was set aside and the filter cake washed with water to provide 5.41 g. (66%) of I, identical in all ways with material prepared by the general procedure.

Evaporation of the filtrate gave a residue which, after repeated crystallization from ethanol, provided 0.3 g. (4.3 %) of 1-(5-nitro-2-furoyl)thiosemicarbazide, identical with authentic[1] material.

Different Colored Modifications of *S*-(*p*-Nitrobenzoyl)acetone Thiosemicarbazone (XI).—This compound could be obtained in either of two colored modifications. When crystallized from benzene, large orange needles were obtained, which melted at 165° dec., turning yellow at about 140°. This material could not be obtained in an analytically pure state. However, if the orange compound was crystallized from ethanol, small yellow needles were obtained of the same melting point. This product gave the analysis shown in Table I. While the yellow form could be induced to crystallize from benzene, only yellow material could be obtained from ethanol. The infrared spectra of the two different colored forms were identical, both in chloroform solution and in Nujol mull.

***S*-(5-Nitro-2-furoyl)-4-benzylidene-1-isopropylidenethiosemicarbazide.**—One-half gram (0.00185 mole) of *S*-(5-nitro-2-furoyl)acetone thiosemicarbazone (I) was covered with a few milliliters of freshly distilled benzaldehyde and the flask flushed with nitrogen. The benzaldehyde was heated at the boiling point until solution occurred. Cooling and scratching provided material which, after crystallization from ethylene glycol dimethyl ether, weighed 0.33 g. (50%) and melted at 213–214°. Repeated crystallization as before gave yellow platelets, m.p. 217°.

Anal. Calcd. for $C_{16}H_{14}N_4O_4S$: C, 53.63; H, 3.94. Found: C, 53.71; H, 3.92.

Solvolysis of Benzylidene Derivative.—To a suspension of 0.23 g. (0.00064 mole) of pure *S*-(5-nitro-2-furoyl)-4-benzylidene-1-isopropylidenethiosemicarbazide in 10 ml. of ethanol was added 1 small drop of concd. hydrochloric acid. When the suspension was heated to the boiling point, solution occurred. Cooling precipitated 0.16 g. (82%) of *S*-(5-nitro-2-furoyl)acetone thiosemicarbazone (I), identical with authentic I in melting point and infrared spectrum.

Nitric Acid and Perchloric Acid Salts of Aminopyridines[1]

C. J. BARNES AND A. J. MATUSZKO

Research and Development Department, U. S. Naval Propellant Plant, Indian Head, Md.

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Very little has been published concerning the preparation and properties of aminopyridine salts with inorganic oxidizer acids. Marckwald[2] reported the preparation of the mononitric acid addition salt of 2-aminopyridine, but no mention was made of reaction conditions or melting point of the product. Monosalts of 2-amino-4-methylpyridine[3] and 2-amino-6-methylpyridine[4] have been prepared by the addition of concentrated nitric acid to an alcoholic solution of the free base. To our knowledge no perchloric acid salts of aminopyridines have been reported.

This paper presents part of a study on amine salts in which the salts of several aminopyridines were prepared through interactions with nitric acid or perchloric acid. The results obtained are shown in Table I. The procedures used were aimed at the isolation, if possible, of the diacid addition compounds, but none were formed. Even electron donating methyl groups in the 6-position or in the 4,6-position did not increase the basicity enough to permit the formation of the diacid salt.

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[1] Published with the permission of the Bureau of Naval Weapons, Navy Department. The opinions and conclusions are those of the authors.

[2] W. Marckwald, *Ber.*, **27**, 1321 (1894).

[3] O. A. Seide, *Ber.*, **57**, 791 (1924).

[4] O. A. Seide, *J. Russ. Phys. Chem. Soc.*, **50**, 534 (1920).