# Nucleophilic Heteroaromatic Substitution. II. Phthalazines

JOHN H. M. HILL* AND JOHN H. EHRLICH[1]

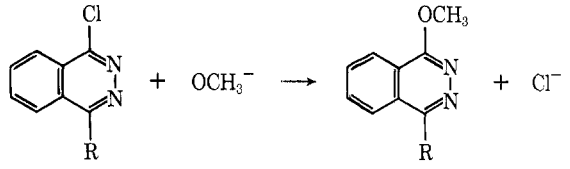
*Department of Chemistry, Hobart and William Smith Colleges, Geneva, New York 14456*

*Received January 18, 1971*

In the current study, we have investigated the kinetics of the methoxydechlorination of a series of 1-chloro-4-substituted phthalazines and related compounds. This parallels an earlier investigation involving 3-chloro-6-substituted pyridazines[2] and was designed, in part, to show the effect of annelation on this ring system.

Nucleophilic reactivity in heteroaromatic systems[3] has been the subject of several extensive reviews, but it appears that no detailed kinetic investigation into the effect of substituents on the reactivity of the phthalazine ring toward methoxydechlorination has been carried out.

In the series of compounds investigated, as in the previous pyridazine series, the annular nitrogens are $\alpha$ and $\beta$ to the leaving group which is chloride and also to the ring substituents, which comprise a series of eight groups displaying various electronic effects.



I–VIII

I, R = Cl; II, R = H; III, R = $C_6H_5$; IV, R = $CH_3$; V, R = $CH(CH_3)_2$; VI, R = $OCH_3$; VII, R = $NH_2$; VIII, R = $O^-$

For the purpose of comparison and to avoid acid catalysis,[4] methoxide was again chosen as the nucleophile and methanol as the solvent. Nevertheless, measurements of the kinetics of the methoxydechlorination were complicated by the fact that methanolysis occurred with I and II when they were dissolved in methanol. Unless extreme precautions were taken to maintain anhydrous conditions, this side reaction became autocatalytic with rapid liberation of ionic chloride. Under strictly anhydrous conditions with freshly prepared solutions of reactants, reproducible bimolecular kinetics were obtained. At the other extreme, VII and VIII reacted very slowly with methoxide, and to obtain appreciable reaction in a reasonable time it was necessary to carry out the reaction at higher temperatures and under pseudo-first-order conditions. The reactions were followed by the rate of liberation of ionic chloride rather than methoxide consumption as was the case with the more reactive compounds. That these methods gave equivalent results was shown by performing both types of determination during the same run for I, II, and VI, when essentially identical rate constants were obtained. This also indicated that in these cases, at least, the leaving group was chloride and that no stable intermediate were participating in the reaction.

The rates of methoxydechlorination were obtained for II, III, IV, and V at 25, 40, and 55°. In addition, VI and VII were determined at 55°, VI, VII, and VIII at 70°, and I at 0, 25, and 40°. Reactions were followed to about half-lives in most cases. For VI at 40° reaction was only followed to about 1 half-life and for VII and VIII, because of the very slow reaction at both temperatures, only as far as 15%. The kinetic parameters calculated from this rate are in Table I.

The expected products of the reaction, 1-methoxyphthalazines, were isolated in excellent yield from I, II, IV, and VI when the reactions were duplicated on a preparative scale. In no cases were the products of self-condensation, 2-(1-phthalazinyl)phthalazin-1-ones, isolated.[5] Such products usually result from an acid-catalyzed reaction which would only be possible if methanolysis occurs before reaction but not when methoxide is present.

Examination of the rate data obtained showed that in all cases the reaction was cleanly first order in methoxide as far as they were followed. In those cases where both phthalazine and methoxide concentrations were both varied, excellent first-order dependence on each reactant was found. The bimolecular nature of the kinetics suggests that the usual SNAr2 mechanism operates.[6] This mechanism, involving a cyclohexadienide intermediate, has been considered to be the major route available for nucleophilic aromatic substitution, both in aromatic and heteroaromatic systems. The alternative heteroaryne mechanism, which has been demonstrated in a few examples of nucleophilic heteroaromatic substitution, cannot operate with 1-chlorophthalazines because of the absence of a proton adjacent to the leaving group.[7]

Satisfactory Hammett plots (Figure 1) were obtained from the rate data using $\sigma_p$ values.[8] The values of $\rho$ obtained are as follows: 25°, +6.15 ($r$ = 0.986); 40°, +6.30 ($r$ = 0.986); 55°, +6.40 ($r$ = 0.897) (this latter correlation includes data for VII which, while not appearing in Figure 1, is well correlated by the regression line). These values are very similar to the value of +6.85 ($r$ = 0.92) found for the methoxydechlorination of 3-chloropyridazines at 40°.[2] The magnitude and sign of $\rho$ shows that the reaction is quite sensitive to the nature of the substituent in the 4 position of the phthalazine ring and that decreased electron density on the ring facilitates the reaction.[9]

Attempts to extend the series to compounds which had stronger electron-withdrawing substituents than those shown above were unsuccessful. For example, it was expected that oxidation of 1-chloro-4-methylphthalazine, by analogy with 3-chloro-6-methylpyrida-

(1) Abstracted, in part, from the B.S. Honors Thesis of J. H. E. Hobart College, 1966.

(2) J. H. M. Hill and J. G. Krause, *J. Org. Chem.*, **29**, 1642 (1964).

(3) G. Illuminati, *Advan. Heterocycl. Chem.*, 285 (1964); R. G. Shepherd and J. L. Fedrick *ibid.*, 145 (1965).

(4) C. K. Banks, *J. Amer. Chem. Soc.*, **66**, 1127 (1947); G. Illuminati, G. Marino, and G. Speiter, *ibid.*, **89**, 3510 (1967).

(5) G. M. Badger, I. J. McCarthy, and H. J. Rodda, *Chem. Ind. (London)*, 964 (1954).

(6) J. Miller, *J. Amer. Chem. Soc.*, **85**, 1628 (1963).

(7) M. J. Pieterse and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas*, **80**, 1376 (1961).

(8) Values used were those of D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

(9) Values as large as +9.2 have been found for some nucleophilic aromatic substitutions [J. Miller, *Aust. J. Chem.*, **9**, 61 (1956)]; values near +5 are usual for annelated heterocyclic systems [M. L. Belli, G. Illuminati, and G. Marino, *Tetrahedron*, **19**, 345 (1963)].

TABLE I

KINETIC DATA FOR THE METHOXYDECHLORINATION OF 1-CHLORO-4-SUBSTITUTED PHTHALAZINES[a]

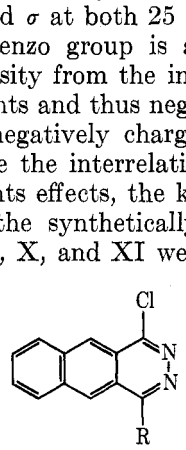
| R | 0° | 25° | 40° | 55° | 70° |
|---|---|---|---|---|---|
| Cl | 261 ± 6 | 2130 ± 30 | 6408 ± 83 | | |
| H | | 51.2 ± 0.7 | 184 ± 3 | 622 ± 5 | |
| $C_6H_5$ | | 37.2 ± 0.4 | 136 ± 5 | 426 ± 6 | |
| $CH_3$ | | 8.6 ± 0.2 | 32.9 ± 0.8 | 106 ± 4 | |
| $CH(CH_3)_2$ | | 10.9 ± 0.3 | 40.9 ± 0.3 | 145 ± 2 | |
| $OCH_3$ | | | 2.64 ± 0.05 | 10.13 ± 0.08 | 36.2 ± 0.13 |
| $NH_2$ | | | | 0.09 ± 0.03 | 0.36 ± 0.02 |
| $O^-$ | | | | | 0.0014 |

[a] $10^4k_2$, l./mol sec.

zine, would yield 1-chlorophthalazine-4-carboxylic acid which could then be converted into the ester,[2] etc. In practice, only 1(2*H*)-phthalazone-4-carboxylic acid could be isolated and attempts to chlorinate this latter compound, independently synthesized, with $POCl_3$ or $PCl_5$ failed to give any isolable product other than starting material.

Comparison of the nonannelated pyridazine and the phthalazine systems shows that where substitution is the same a rate enhancement is observed in the annelated system. Such an annelation effect has been observed in other nucleophilic heteroaromatic systems. For example, comparison of 2-chloropyridine and 1-chloroisoquinoline shows that the latter is 310 times as reactive to ethoxydechlorination,[10] while a similar comparison between 4-chloropyridine and 4-chloroquinoline shows a rate enhancement of 7.5.[11] The present system shows rate enhancements of from about 50- to 100-fold.

These increases in reactivity can be attributed to the expanded region available through which the negative charge can be delocalized in the transition state. A more detailed examination of the rate enhancements shows that they are dependent on the nature of the substituent with the greatest effect occurring with the most electron-donating substituents. An approximately linear relation exists between the log of the ratio of the rate constants for similarly substituted phthalazines and pyridazines and $\sigma$ at both 25 and 40° (Figure 2). Presumably the benzo group is able to absorb the added electron density from the increasingly electron-donating substituents and thus negate their destabilizing effect on the negatively charged transition state. To further examine the interrelation between annelation and substituents effects, the kinetics of methoxydechlorination of the synthetically accessible benzo[*g*]phthalazines IX, X, and XI were studied briefly.[12]




IX, R = Cl
X, R = H
XI, R = $OCH_3$

Rate data for these compounds is in Table II. It can be seen that further annelation increases the rate of methoxydechlorination to a lesser extent, but that the same trend regarding the effect of substituents is maintained with the methoxy group producing a greater rate enchancement than the chlorine.

Activation of the heterocyclic ring to nucleophilic attack is a consequence of the interaction of the annular nitrogens with the developing negative charge in the transition state. It has been shown that aza substitution activates attack by the nucleophile at the carbon bearing the leaving group with $\alpha$ and $\gamma$ substitution being more effective than $\beta$ substitution.[13] Although both $\alpha$ and $\gamma$ nitrogens activate by conjugative interaction with

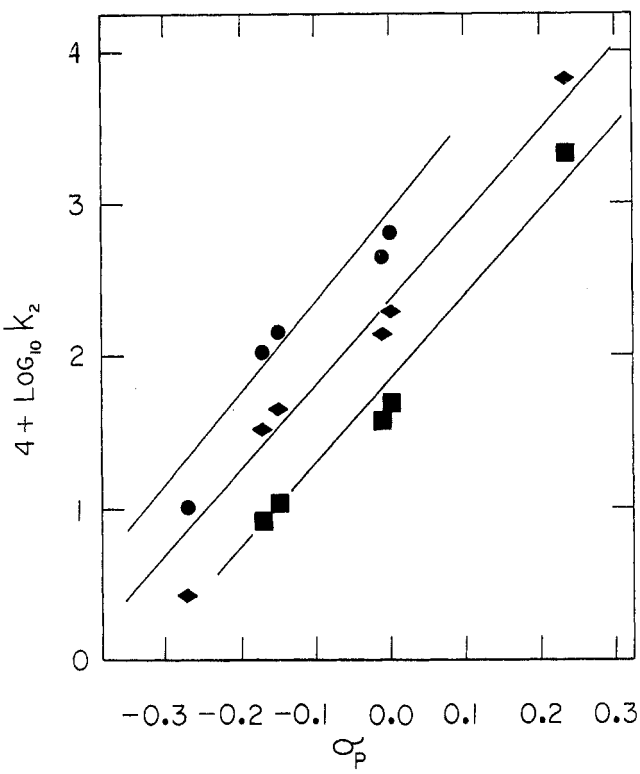



Figure 1.—Hammett plot (log $k$ *vs.* $\sigma_p$) for the reaction of 1-chloro-4-substituted phthalazines with methoxide: ●, 55°; ◆, 40°; ■, 25°.

TABLE II

KINETIC DATA FOR THE METHOXYDECHLORINATION OF 1-CHLORO-4-SUBSTITUTED BENZO[*g*]PHTHALAZINES[a]

| R | 0° | 25° | 40° |
|---|---|---|---|
| Cl | 1130 ± 50 | 8047 ± 130 | |
| H | | 279 ± 5 | 927 ± 23 |
| $OCH_3$ | | 6.06 ± 0.36 | 23.8 ± 1.7 |

[a] $10^4k_2$, l./mol sec.

(10) K. R. Brower, J. W. Way, W. P. Samuels, and E. D. Amstutz, *J. Org. Chem.*, **19**, 1830 (1954).
(11) N. B. Chapman and D. Q. Russell-Hill, *J. Chem. Soc.*, 1563 (1956).
(12) H. D. K. Drew and R. F. Garwood *ibid.*, 836 (1939).
(13) M. Liveris and J. Miller, *ibid.*, 3486 (1963).

TABLE III
THERMODYNAMIC DATA FOR THE METHOXYDECHLORINATION OF 1-CHLORO-4-SUBSTITUTED PHTHALAZINES

| R | Cl | H | $C_6H_5$ | $CH_3$ | $CH(CH_3)_2$ | $OCH_3$ | $NH_2$ |
|---|---|---|---|---|---|---|---|
| $\Delta H^*$, kcal/mol | 13.1 | 15.2 | 15.4 | 16.0 | 16.6 | 18.1 | 20.2 |
| $\Delta S^*$, cal/deg mol | −17.9 | −18.0 | −18.0 | −19.0 | −16.6 | −17.5 | −20.4 |

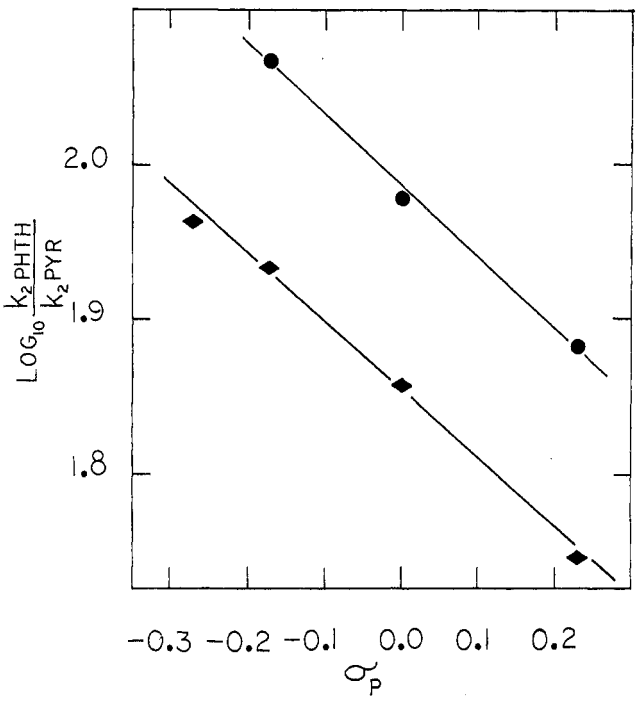



Figure 2.—Relationship between $\sigma_p$ and the log of ratio rates of substitution for phthalazines and pyridazines: ◆, 40°; ●, 25°.

the negative charge, $\gamma$ substitution is generally more efficient with anionic nucleophiles in hydroxylic solvents, because interaction between the nitrogen lone pair and the approaching nucleophile is minimized; $\beta$ substitution allows only inductive activation. This latter effect has been shown to be appreciable.[2,14] With phthalazines in methanol, the effect of the $\alpha$ nitrogen is essentially constant and it is the electron demand of the substituent para to the leaving group which controls the variation in reaction rate. Modification of the substituent effect by its interaction with the benzo group and by conjugative interaction with the $\beta$ nitrogen also occurs. This is turn modifies the inductive effect of the $\beta$ nitrogen. The thermodynamic parameters obtained in this study are unexceptional and lie in the range normally found for bimolecular reactions of a negatively charged nucleophile with an aromatic substrate. The rise in activation ethalpy with increased electron donation from the substituent appears to be the major reason for the change in reaction rate as the activation entropy remains essentially constant throughout the series. Consequently, the stability of the transition state is a function of the electronic demands of the substituent. The thermodynamic parameters are included in Tables III and IV.

## Experimental Section

**Materials.**—Dry methanol and sodium methoxide in dry methanol were stored in the absence of carbon dioxide and moisture and dispensed from burets fitted with Teflon stopcocks. All solutions were prepared and transferred under dry nitrogen. One batch of methoxide was used throughout the experimental work. Periodic analysis of aliquots showed no change in concentration and no evidence of formation of carbonate during a 2-month period.

(14) K. R. Brower, W. P. Samuels, J. W. Way, and E. D. Amstutz, *J. Org. Chem.*, **18**, 1648 (1953).

TABLE IV
THERMODYNAMIC DATA FOR THE METHOXYDECHLORINATION OF 1-CHLORO-4-SUBSTITUTED BENZO[*g*]PHTHALAZINES

| R | Cl | H | $OCH_3$ |
|---|---|---|---|
| $\Delta H^*$, kcal/mol | 12.7 | 14.8 | 16.9 |
| $\Delta S^*$, cal/deg mol | −16.3 | −16.4 | −16.8 |

The phthalazines were prepared by published procedures and were purified by several recrystallizations from the solvents specified: 1,4-dichlorophthalazine (I) from benzene–hexane, mp 164° (lit.[15] mp 164–165°); 1-chlorophthalazine (II) from hexane, mp 119–120° (lit.[16] mp 113°); 1-chloro-4-phenylphthalazine (III) from benzene, mp 161–163° (lit.[17] mp 160–161°); 1-chloro-4-methylphthalazine (IV) from benzene–hexane, mp 132° (lit.[18] mp 129–130); 1-chloro-4-isopropylphthalazine (V) from ethanol, mp 81–82° (lit.[19] mp 81–83°); 1-chloro-4-methoxyphthalazine (VI) from benzene, mp 107–108° (lit.[20] mp 107–108°), 1-amino-4-chlorophthalazine (VII) from ethanol, mp 201–202° (lit.[21] mp 202°); 1-chloro-4(3*H*-)phthalazone (VIII) from acetic acid, mp 271° (lit.[22] mp 274°).

**1,4-Dichlorobenzo[*g*]phthalazine (IX).**—A mixture of 2,3-dihydrobenzo[*g*]phthalazine-1,4-dione[2] (21.2 g, 0.1 mol), phosphoryl chloride (180 ml), and phosphorus pentachloride (46 g, 0.22 mol) was heated gently for 3 hr. The resulting homogeneous solution was distilled to remove most of the phosphoryl chloride and the residue was added cautiously to an ice-cold saturated aqueous solution of sodium bicarbonate. The solid was extracted into methylene chloride, washed with several portions of ice-cold saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The residue was recrystallized twice from chloroform–hexane to yield IX as almost white needle-shaped crystals, 14.7 g (59%), mp 258–261° dec.

*Anal.* Calcd for $C_{12}H_6N_2Cl_2$: N, 11.24; Cl, 24.46. Found: N, 11.44; Cl, 24.12.

**1-Chlorobenzo[*g*]phthalazine (X).**—A suspension of IX (5.0 g, 0.02 mol) in dilute hydrochloric acid (100 ml of 6 *M*) was refluxed for 3 hr. The mixture was cooled and adjusted to pH 9 with sodium carbonate, and the 1-chloro-4(3*H*)-benzo[*g*]phthalazone was filtered. Without purification it was dissolved in glacial acetic acid (200 ml), which contained sodium acetate (1.65 g, 0.02 mol) and this solution was shaken with 10% palladium on carbon (0.5 g) under hydrogen at 3 atm. Uptake of hydrogen essentially ceased after 12 hr. The solution was heated, filtered to remove catalyst, and evaporated until crystals began to appear. Cooling resulted in precipitation of 1(2*H*)-benzo[*g*]phthalazine as a white powder, 2.2 g (56%), mp over 300°.

This product was dissolved in phosphoryl chloride (50 ml) and phosphorus pentachloride (2.5 g, 0.012 mol) was added. The mixture was refluxed for 3 hr, the bulk of the phosphoryl chloride was distilled, the residue was shaken with an ice-cold mixture of saturated sodium bicarbonate solution, dried ($MgSO_4$), and evaporated, and the residue crystallized from benzene.

(15) J. A. Elridge and A. P. Redman, *J. Chem. Soc.*, 1710 (1960).
(16) S. Gabriel and A. Neuman, *Ber.*, **26**, 521 (1893).
(17) A. Leick, *ibid.*, **38**, 3918 (1905).
(18) E. F. M. Stephenson, *J. Chem. Soc.*, 1913 (1963).
(19) A. Aebi, *Pharm. Acta Helv.*, **40**, 241 (1965).
(20) S. Biniecki and J. Izdebski, *Acta Pol. Pharm.*, **15**, 421 (1957); *Chem. Abst.*, **52**, 15540*g* (1958).
(21) I. Satoda, F. Kusada, and K. Mori, *Yakugaku Zasshi*, **82**, 233 (1962); *Chem. Abstr.*, **58**, 3437*e* (1963).
(22) H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, **16** (1937).

1-Chlorobenzo[*g*]phthalazine was isolated as tan crystals, 0.7 g (16% overall), mp 178–180°.

*Anal.* Calcd for $C_{12}H_7N_2Cl$: N, 13.05; Cl, 16.52. Found: N, 12.84; Cl, 16.18.

**1-Chloro-4-methoxybenzo[*g*]phthalazine (XI).**—A solution of sodium (0.23 g, 001 g-atom) in methanol (150 ml) was treated with IX (2.49 g, 0.01 mol). The mixture was refluxed under nitrogen for 2 hr and then concentrated to dryness *in vacuo*. The residue was extracted with boiling methylene chloride (100 ml), evaporated to dryness *in vacuo*, and recrystallized from benzene to yield XI as tan crystals, 1.66 g (68%), mp 134–136°.

*Anal.* Calcd for $C_{13}H_9N_2OCl$: N, 11.44; Cl, 14.49. Found: N, 11.37; Cl, 14.19.

**Kinetics.**—The procedure, using a divided flask, was essentially as previously described except that the flask was closed with a septum through which aliquots for estimation were removed by calibrated syringe.[2] For runs at 70° a standard sealed ampoule method was employed. To measure the reaction rates for IX at 0°, V, X, and XI at 25°, III at 55°, and VI at 70°, aliquots for estimation were partitioned between a known volume of 0.1 *M* perchloric acid and methylene chloride. The chloride ion concentration in the aqueous phase was determined using a specific ion electrode (Orion Model 92-17) and a Beckman Expandomatic pH meter, and calibration curves were prepared from standard chloride ion solutions. As before, runs were made in triplicate and the concentrations varied by a factor of 4 with respect to each other except for those compounds run under pseudo-first-order conditions.

**Calculations.**—The rate constants were obtained from a least-squares analysis of the relevant expressions: $\ln a/(a - x)$ or $[1/(b - a)] \ln [a(b - x)/b(a - x)]$ *vs.* time. Calculations were carried out on an IBM 1130 computer. $\Delta H^*$ and $\Delta S^*$ were determined as described by Bunnett.[23]

**Product Analysis.**—The products of the reaction of I, II, IV, and VI were obtained from reactions of 0.01 mol of these phthalazines with an equimolar amount of sodium methoxide in methanol. The solvent was evaporated and the residue extracted with boiling methylene chloride. Evaporation and recrystallization from benzene yielded the products: from I, 1-chloro-4-methoxyphthalazine (66%), mp 107–108° (lit.[20] mp 107–108°); from II, 1-methoxyphthalazine (82%), mp 61–62° (lit.[17] mp 60–61°); from IV, 1-methoxy-4-methylphthalazine (71%), mp 71–72° (lit.[24] mp 53–54°), and 1,4-dimethoxyphthalazine (81%), mp 93° (lit.[15] mp 93°).

**Registry No.**—I, 4752-10-7; II, 5784-45-2; III, 10132-01-5; IV, 19064-68-7; V, 2258-89-1; VI, 19064-71-2; VII, 13580-86-4; VIII, 2257-69-4; IX, 30800-67-0; X, 30800-68-1; XI, 30800-69-2.

(23) J. F. Bunnett, *Tech. Org. Chem.*, **8**, 199 (1961).

(24) F. M. Rowe and A. T. Peters, *J. Chem. Soc.*, 1331 (1933). The nmr spectrum was consistent with the structure: $\delta$ 2.36 (s, 3 H, $CH_3$), 3.84 ppm (s, 3 H, $OCH_3$).

## Synthesis of Tris(carboalkoxyamino)methane and *N*-Carbethoxyiminocarboxylic Acid Esters[1]

VYTAUTAS GRAKAUSKAS

*Fluorochem, Inc., Azusa, California 91702*

*Received March 24, 1971*

Only a few tris(amino)methane derivatives of the general structure $HC(NHR)_3$ are known. Tris(formamido)methane (*N*,*N*′,*N*″-methylidynetrisformamide) and tris(acetamido)methane were reported by Pinner[2] in 1883. Several higher homologs of this series were recently synthesized by Bredereck, *et al.*,[3] by heating ethyl orthoformate with amides in the presence of a catalytic amount of sulfuric acid.

We have now synthesized tris(carboalkoxyamino)methanes by heating ethyl orthoformate with alkyl carbamates and using aniline sulfate as the catalyst.

$$HC(OC_2H_5)_3 + NH_2COOR \xrightarrow[\Delta]{\text{aniline sulfate}} HC(NHCOOR)_3 + C_2H_5OH$$
$$R = CH_3, C_2H_5$$

The compounds, obtained in 45–55% yields, were characterized by elemental analysis and nmr spectra. The proton nmr spectrum of tris(acetamido)methane (see Experimental Section) is similar to that of tris(carbethoxyamino)methane.

Reactions of higher ortho esters with urethane under similar reaction conditions were found to give different products. Thus, urethane reacted with triethyl orthoacetate or triethyl orthopropionate to give ethyl *N*-carbethoxyacetimidate and ethyl *N*-carbethoxypropioimidate, respectively. *N*-Carbethoxyiminocarboxylic acid esters are colorless liquids, sparingly soluble in water, and stable at room temperature.

$$RC(OC_2H_5)_3 + NH_2COOC_2H_5 \xrightarrow[\Delta]{\text{aniline sulfate}} RC(OC_2H_5)=NCOOC_2H_5$$
$$R = CH_3, C_2H_5$$

### Experimental Section

**Tris(carbethoxyamino)methane.**—A mixture containing 40 g (0.27 mol) of ethyl orthoformate, 74 g (0.81 mol) of ethyl carbamate, and 0.7 g of aniline sulfate was heated in a distillation apparatus at 115–125° for 2.5 hr. During this time 32 ml of ethanol distilled over. The temperature was then increased to 155° for 1.5 hr, and an additional 13 ml of ethanol was removed. The reaction mixture was cooled and the crude material was recrystallized from methylene chloride to give 41 g (55% yield) of tris(carbethoxyamino)methane, a white, crystalline solid, mp 210–211°.

*Anal.* Calcd for $C_{10}H_{19}N_3O_6$: C, 43.31; H, 6.91; N, 15.16. Found: C, 43.11; H, 6.82; N, 15.03.

Proton nmr (DMSO-$d_6$) showed $\delta$ 7.45 (d, $J$ = 7.0 Hz, 3, NH), 6.24 (q, $J$ = 7.0 Hz, 1, CH), 4.03 (q, $J$ = 7.1 Hz, 6, $CH_2$), and 1.20 (t, $J$ = 7.0 Hz, 9, $CH_3$).

The proton nmr spectrum (DMSO) of tris(acetamido)methane showed $\delta$ 7.42 (d, $J$ = 7.2 Hz, 3, NH), 6.12 (q, $J$ = 7.0 Hz, 1, CH), and 3.62 (s, 9, $CH_3$).

**Tris(carbomethoxyamino)methane.**—The title compound was synthesized from ethyl orthoformate and methyl carbamate in 45% yield following the above procedure. The crude solid was crystallized from methanol, mp 177–178°.

*Anal.* Calcd for $C_7H_{13}N_3O_6$: C, 35.74; H, 5.57; N, 17.87. Found: C, 36.11; H, 5.62; N, 17.81.

In a separate experiment, a mixture of ethyl orthoformate and methyl carbamate was heated at 145° for 2 hr in the absence of aniline sulfate. No ethanol was liberated and only the starting materials were isolated from the reaction mixture at the end of the experiment.

**Ethyl *N*-Carbethoxyacetimidate.**—A mixture containing 32.5 g (0.2 mol) of ethyl orthoacetate, 60 g (0.4 mol) of ethyl carbamate, and 0.7 g of aniline sulfate was heated in a distillation apparatus at 110–120° for 1.5 hr. During this time 20 ml of ethanol was distilled. The reaction mixture was cooled to 5° and the excess of ethyl carbamate was removed by filtration. The filtrate was dissolved in 150 ml of carbon tetrachloride and the solution was washed with four 100-ml portions of water in order to remove the remaining ethyl carbamate. The carbon tetrachloride solution was distilled to give 21 g (66% yield) of a colorless liquid, bp 90–91° (25 mm).

*Anal.* Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.51; H, 8.61; N, 8.97.

(1) This work was supported by the Office of Naval Research. The experimental work was performed at the Aerojet-General Corp., Azusa, Calif.

(2) A. Pinner, *Ber.*, **16**, 357, 1647, 1660 (1883); **17**, 172 (1884).

(3) H. Bredereck, F. Effenberger, and H. J. Treiber, *ibid.*, **96**, 1505 (1963).