Synthesis of Hexahydro 1,3,5-triCarbalkoxy-*s*-triazines, Octahydro-1,3,5,7-tetracarbalkoxy Tetrazocines and Their Interconvertibility

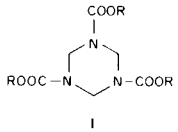
B. S. Thyagarajan, and K. C. Majumdar*

Chemistry Department, University of Idaho, Moscow, Idaho 83843

Received May 28, 1974

The condensations of urethanes with formaldehyde under appropriate experimental conditions affords either 1,3,5-triazines or 1,3,5,7-tetrazocines. The two systems are interconvertible under acid catalysis.

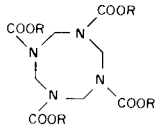
The condensation of urethanes with formaldehyde has been known since the beginning of this century, to give rise to methylenediurethanes (1,2). In later work, Giua and Facciu (3) reported the reaction product as a trimer *viz.* the triazine derivative (I).



I

R C_2H_5

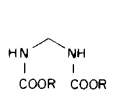
The triazine structure I was confirmed by Marvel, Elliott, Boettner and Yuska (4) in another study related to urea-formaldehyde polymers. However, Giua and Racciu (3) claimed that they also obtained the tetrazocine derivative (II) by evaporating an acetic acid solution of the crude triazine product on a sandbath.



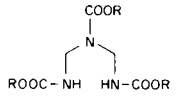
II

R C_2H_5

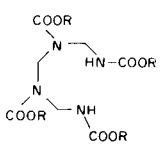
Although ammonoacetals undergo facile acid-catalyzed reorganization (5), this claim to conversion of the triazine I into the tetrazocine II appeared unusual and merited reinvestigation. We undertook a study of 1) the conditions under which urethanes and formaldehyde react to produce either I or II (or a mixture of both); 2) the feasibility of I being transformed into II and II into I; and 3) the possibility of arresting such a reaction at will, at the following stages *viz.* III → IV → V.



III



IV



V

We have effected a marked improvement in the synthesis of *N,N'*-methylenebis(alkyl carbamates) (III) so that these derivatives are secured in very high yields without contamination from any of the other products. This is achieved by stirring the alkyl carbamates with aqueous formalin and concentrated hydrochloric acid in water at room temperature for 24 hours (6).

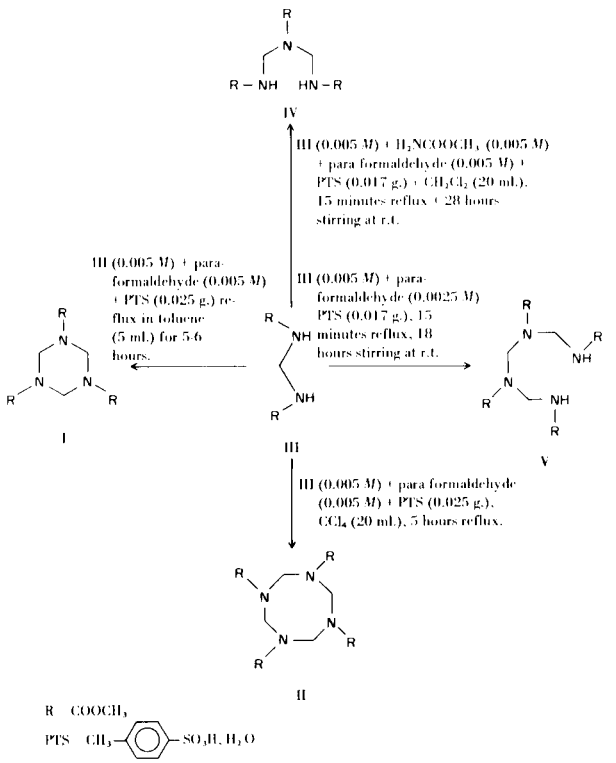
However, when the same urethanes were refluxed with para-formaldehyde and *p*-toluenesulfonic acid in carbon tetrachloride or in toluene over 5 to 6 hours, the reaction course changed completely. The products are now the triazines obtained in very high yields (88-91%, see experimental). A small amount of the tetrazocine can also be *detected* in the crude reaction mixture by nmr and successfully isolated by chromatography. When the reaction time is increased to 16 hours, the yield of triazines increased and the occurrence of the tetrazocine diminished. This suggested the possibility that any tetrazocine formed in the above condensation was prone to modification. If this were true, shortening the reaction time should reveal the formation of larger amounts of the tetrazocine II. This was indeed the case. When III was refluxed in chloroform for 30 minutes or 45 minutes, the tetrazocine, from being a barely detectable impurity, became a major constituent (50%) of the reaction product which now showed only 16% of the triazine and some 33% of other constituents, most likely the uncyclized intermediates like III or V.

These results indicated the possibility of subtle variations in the nature and yields of the different condensation products from urethanes and paraformaldehyde. Some of these reactions are described in the sequel.

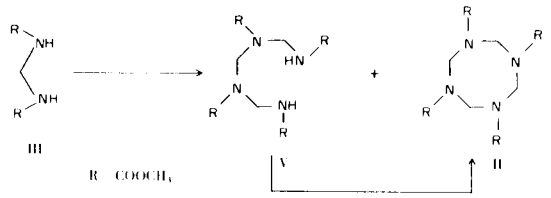
Stirring at ambient temperatures but for longer duration (28 hours) afforded 46-47% of unreacted III and 48% of IV. These were easily separated by chromatography over

silica gel. There was no trace of I, II or V in this reaction. The same condensation carried out at ambient temperatures but for only 18 hours afforded an interesting result. The product mixture showed neither, I, nor II nor IV but a mixture of only III and V, with the latter predominating (67% yields). Scheme I shown below summarizes these observations.

SCHEME I



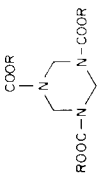
Thus, conditions were found for selectively obtaining, I, IV and V but not II. This was readily remedied by refluxing V with additional quantities of paraformaldehyde in carbon tetrachloride. The tetrazocine was formed in 45% yields. It is also possible to obtain the tetrazocine II, along with uncyclized 1,3,5,7-tetraaza-1,3,5,7-tetracarbomethoxyheptane (V) by refluxing III with paraformaldehyde and *p*-toluenesulfonic acid for only 30 minutes. These observations are summarized in the following equation:



Although a tetrazocine was reported to be formed by Giua and Racciu (3), it was poorly characterized. Since that time, a tetrazocine from the condensation of urethane and paraformaldehyde had not been described. Thus, the

TABLE I

1,3,5-Tricarbalkoxyhexahydro-*s*-triazine

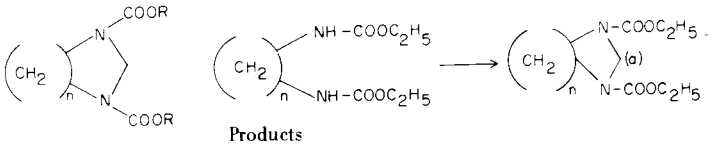


	R	M.P. or B.P. (°C)	% Yield	Molecular Formula	Calcd. C	Calcd. H	Anal. % N	Found C	Found H	Found N	Nmr (in δ): (a) in deuteriochloroform
1	CH_3	121	88	$C_9H_{15}N_3O_6$	41.38	5.74	16.09	41.18	5.77	15.96	5.11 (S, 6H)
2	C_6H_5-CH_2	92	91	$C_{27}H_{27}N_3O_6$	66.26	5.52	8.59	66.30	5.51	8.39	5.23 (S, 6H)
3	$CH_3CH_2CH_2$	67-68	89	$C_{15}H_{27}N_3O_6$	52.17	7.82	12.17	52.21	7.79	12.00	5.14 (S, 6H)
4	H_3C CH H_3C	100-101	89	$C_{15}H_{27}N_3O_6$	52.17	7.82	12.17	52.02	7.82	11.98	5.10 (S, 6H)
5	$CH_3CH_2CH_2CH_2$	140/0.008 mm (b)	90	$C_{18}H_{33}N_3O_6$	55.81	8.53	10.85	55.87	8.53	10.76	5.10 (S, 6H)
6(a)	C_2H_5	102-103	89.6	$C_{12}H_{21}N_3O_6$	47.52	6.93	13.86	47.44	7.02	14.12	5.11 (S, 6H)

(a) Reference 3 and 4. (b) Distilled using a short path distillation apparatus and the b.p. is uncorrected.

TABLE II

Products of Cyclization of Polymethylene Diurethanes



Products

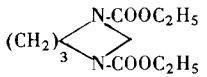
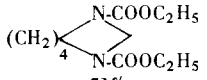
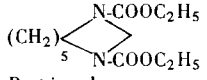
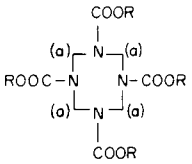
Starting diurethanes			Result		M.P. or B.P.	Molecular	Anal. %						Nmr (in δ)	Ir (Neat):	Molecular ion
							Calcd.			Found			(a)	>= O	peak at m/e
n	M.P. (°C)	% Yield			(°C)	Formula	C	H	N	C	H	N	in deuteriochloroform	(cm^{-1})	
3 (10a)	41-42	87	 95.6%		102-104/0.02 mm	$C_{10}H_{18}N_2O_4$	52.17	7.82	12.17	51.92	7.82	12.34	4.98	1685	230
4 (10b)	93-94	63	 51% Rest is polymer		107/0.04mm	$C_{11}H_{20}N_2O_4$	54.10	8.19	11.47	53.95	8.12	11.68	4.98	1700	244
5 (10c)	70-71	70.7	 Rest is polymer	10%	20-21 127/0.06mm	$C_{12}H_{22}N_2O_4$	55.81	8.52	10.85	55.69	8.58	10.55	4.98	1695	258
6 (10d)	84-85	83.4	Polymer												
7	62	72.4	Polymer												
8 (10e)	82-83	93	Polymer												

TABLE III

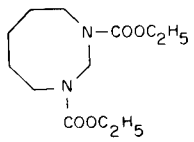
1,3,5,7-Tetracarbalkoxyoctahydrotetrazocines



R	M.P. or B.P. (°C)	% Yield	Molecular Formula	Anal. % Calcd. C	H	N	Found C	H	N	Nmr (in δ) (a) in deuteriochloroform	Ir (Neat): >=O (cm^{-1})	Molecular ion peak at m/e
1. CH_3	113	84	$C_{12}H_{20}N_4O_8$	41.38	5.74	16.09	41.10	5.74	15.92	5.00	1700	348
2. C_2H_5	145-155°/0.01 mm (b)	88	$C_{16}H_{28}N_4O_8$	47.52	6.93	13.86	47.60	7.19	13.58	4.99	1708	404
3. n-C_3H_7	150°/0.01 mm (b)	80	$C_{20}H_{36}N_4O_8$	52.17	7.82	12.17	52.30	7.88	12.05	4.98	1705	460
4. n-C_4H_9	150°/0.01 mm (b)	80	$C_{24}H_{44}N_4O_8$	55.81	8.53	10.85	56.12	8.72	10.58	4.97	1700	516

(b) Compounds 2-4 were distilled under reduced pressure using a short path distillation apparatus and the b.p.'s were not corrected.

present study describes for the first time mild experimental conditions for obtaining tetrazocines in high yields. Although six membered rings are synthesized most readily, cyclization of open chain compounds like V into eight membered rings is not normally anticipated to be a high yield process. The present study in the synthesis of II is therefore quite striking. In order to determine how much of this facility of cyclization stems from the larger number of heteroatoms present in the openchain derivative, we undertook a study of the behavoir of polymethylene diurethanes with formaldehyde, under comparable conditions. The eight membered ring with only two nitrogens (VI) was formed in yields of only 10% in striking contrast to the high yields of II from III. These results are summarized in Table II.



VI

These results clearly demonstrate the strikingly impressive variations in the formation of open chain compounds, triazines and/or tetrazocines from the simple acid catalyzed condensation of urethanes with paraformaldehyde. Some of these reactions do indicate the greater yields of the triazines at higher temperatures and longer durations of reaction. Could this suggest that II was degrading into I under the experimental conditions? The tetrazocines are completely stable to heat alone. In the presence of a trace of acid, however, their stability to heat is lost, resulting in facile conversion to the triazines. Is this ring contraction a simplistic elimination of a methylene urethane moiety from II or is it a *total* degradation of II into formaldehyde and urethane, followed by a resynthesis into the triazine I? This question is amenable to verification by posing the same question in another fashion. If the formation of the triazine from the tetrazocine involved total degradation, then it should also be possible to form tetrazocines from the degradation of triazines, as it is well demonstrated elsewhere in this study that tetrazocines do form in high yields from paraformaldehyde and urethanes at ambient temperatures. We examined this possibility. Most surprisingly and in remarkably high yields, triazines (I) do transform into tetrazocines II. These results observed in four different examples are summarized in Table III.

To our knowledge, this is the first example of such facile reorganization of triazines into tetrazocines. These results reinforce our related studies on the acid catalyzed reorganizations of azaanalogs of adamantane derived from sulfamide and formaldehyde (5,7).

In summary, condensation of urethanes with formaldehyde under acid catalysis affords a variety of products, depending upon the reaction temperature and length of reaction time. Products of such condensation are capable of reversal to their constituent components and resynthesis to simple or complex products. Synthesis of eight-membered rings with four nitrogen atoms is more facile than the synthesis of the same ring with only two nitrogen atoms. Thus medium ring synthesis is rendered more facile by the incorporation of hetero atoms in the openchain derivative.

EXPERIMENTAL

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and were not corrected. Nuclear Magnetic Resonance (nmr) spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectral data were obtained on a Hitachi-Perkin-Elmer RMU-6E single focus low resolution instrument at 70 e.v. and 20 e.v. Microanalyses were performed in this department.

Synthesis of Methanediurethanes.

The alkyl carbamate (0.25 mole) was dissolved in water (30 ml. for methyl carbamate, 100 ml. for ethyl carbamate, 450 ml. for *n*-propyl carbamate and 650 ml. for isopropyl carbamate). Then 37% formalin (10 ml.) and concentrated hydrochloric acid (1 ml. for methyl carbamate, 1.5 ml. for ethyl carbamate, 2.5 ml. for *n*-propyl carbamate and isopropyl carbamate) were added and the mixture stirred at room temperature for 24 hours to give a white crystalline solid. The solid was filtered, washed well with water and dried. The solid was recrystallized from ether-pertoleum ether (30-60°) or from 95% ethanol.

	M.P. (°C)	% Yield
1. Methanedi-(methylcarbamate) (8)	124-125	81
2. Methanediurethane (1,8)	130-131	84
3. Methanedi-(*n*-propyl carbamate) (8)	114	90
4. Methanedi-(isopropyl carbamate) (8)	151	85

Synthesis of Methanedi(benzylcarbamate).

Benzyl carbamate (30.2 g., 0.2 mole), paraformaldehyde (3.0 g., 0.1 mole), and *p*-toluenesulfonic acid (0.40 g.) were refluxed in methylene chloride for 30 minutes. More chloroform (300 ml.) was added and the solution was washed with 5% sodium hydroxide solution, water and was dried (sodium sulfate). Removal of solvent gave a *white solid* which was recrystallized from methylene chloride-petroleum either (30-60°), yield 25.2 g. (80%); m.p. 154°; nmr (deuteriochloroform): δ 4.40-4.65 (t, 2H), 5.10 (S, 4H), 5.65-6.00 (broad, 2H), 7.35 (S, 10H); MS: molecular ion peak at m/e 314.

Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.73; N, 8.91. Found: C, 64.69; H, 5.63; N, 8.81.

Synthesis of 1,3,5-Tricarbalkoxyhexahydro-*s*-triazines.

Carbamic ester (0.02 mole), paraformaldehyde (0.70 g.) and *p*-toluenesulfonic acid monohydrate (0.1 g.) were refluxed in toluene (10 ml.) for 5-6 hours. The solvent was removed under a vacuum. The white solid (compounds 1, 3, 4, 6 of Table I) or viscous oil (compounds 2 and 5 of Table I) was dissolved in chloroform (150 ml.). The chloroform solution was washed with dilute sodium hydroxide solution, salt water and dried (sodium sulfate).

Removal of solvent gave a white solid or a colorless viscous oil. The solids were recrystallized from ether-petroleum ether (30-60°) or from ethanol. The liquids were purified by chromatography over silica gel using benzene-acetone 5:1 as eluting solvent. Then the liquids were distilled under a vacuum using a short path distillation apparatus. The compounds thus obtained are listed in Table I. The 1,3,5-tricarbalkoxyhexahydro-*s*-triazines are also obtained when methanedialkyl carbamates (0.01 mole), paraformaldehyde (0.01 mole) and *p*-toluenesulfonic acid (0.05 g.) were refluxed in toluene (10 ml.) for 5-6 hours or in carbon tetrachloride (10 ml.) for 12 hours or in chloroform (10 ml.) for 16-20 hours.

Reaction of Methanedi(methylcarbamate) with Paraformaldehyde in Presence of *p*-Toluenesulfonic Acid in Refluxing Chloroform for 30 Minutes and 45 Minutes.

Methanedi(methylcarbamate) (0.81 g., 0.005 mole), paraformaldehyde (0.08 g., 0.0025 mole) and *p*-toluenesulfonic acid (0.02 g.) were refluxed in chloroform (10 ml.) for 30 minutes. The nmr spectrum of the solution indicated the presence of ~36% of tetrazocine derivative, ~64% of a mixture of open chain compound V (Major) and starting material (minor). When the above reaction mixture was refluxed with additional para-formaldehyde (0.08 g.) for 30 minutes more, the nmr spectrum showed a mixture of 15% of triazine derivative, ~50% of tetrazocine derivative and ~35% of open chain compound.

When methanedi(methylcarbamate) (0.81 g., 0.005 mole), paraformaldehyde (0.16 g., 0.005 mole) *p*-toluenesulfonic acid (0.02 g.) were refluxed in chloroform for 45 minutes, the nmr spectrum of the solution indicated this to be a mixture of ~16% triazine derivative, ~50% tetrazocine derivative and 33% open chain compound.

Nmr Studies of the Formation of Tetrazocine Derivative from Methanediurethane and Paraformaldehyde in the Presence of *p*-Toluenesulfonic Acid and its Conversion to Triazine Derivative with Time in the Same Reaction Medium.

Methanediurethane (1.90 g., 0.01 mole), paraformaldehyde (0.30 g., 0.01 mole) and *p*-toluenesulfonic acid (0.05 g.) were refluxed in chloroform (10 ml.) and aliquots were taken out in intervals to record the nmr spectrum.

Time of reflux (in hours)	~% Triazine	~% Tetrazocine
1	60	35
1.5	68	28
2	74	22
3	80	17
4	84	13
5	86	11
7	90	7
8	93	4

Synthesis of 1,3,5-Tricarbomethoxy-1,3,5-triazapentane (IV).

Methanedi(methylcarbamate), III (0.81 g., 0.005 mole), methyl carbamate (0.375 g., 0.005 mole), paraformaldehyde (0.16 g., 0.005 mole) and *p*-toluenesulfonic acid (0.017 g.) were refluxed in methylene chloride (20 ml.) for 15 minutes. Then the reaction mixture was stirred at room temperature for 28 hours. More solvent (chloroform, 100 ml.) was added. The solution was washed with dilute NaOH solution, salt water and dried (sodium sulfate). Removal of solvent gave a colorless oil. The nmr spectrum of the crude product indicated three components in it, ~50% 1,3,5-tricarbomethoxy-1,3,5-triazapentane, ~46-47% starting material methanedi(methylcarbamate) and very little (~1-2%) of 1,3,5,7-tetracarbomethoxy-1,3,5,7-tetraazaheptane. This oil was triturated with ether-petroleum ether (30-60°) mixture to give a solid, which is unreacted methanedi(methylcarbamate). The residual oil was then chromatographed through a silica gel column (47 x 2.0 cm) and eluted with benzene acetone 4:1 mixture.

The first 2 x 100 ml. of eluent gave the rest of the unreacted methanedi(methylcarbamate). Next 2 x 100 ml. portions gave 1,3,5-tricarbomethoxy-1,3,5-triazapentane 0.60 g., 48.4%. This compound is an oil, could not be solidified even by further chromatographic purification. This compound has the following spectral data, nmr (deuteriochloroform): 3.68 δ (s, 6H), 3.75 δ (s, 3H), 4.65-4.85 δ (d, 4H), 5.85-6.30 (broad, 2H), on adding deuterium oxide the broad peak at 5.85-6.30 δ disappeared and the doublet at 4.65-4.85 δ collapsed to a singlet; ir (neat): 1705 cm^{-1} (>C=O); MS: molecular ion peak at m/e 249 (p) and 250 (p + 1).

Anal. Calcd. for $C_8H_{15}N_3O_6$: C, 38.55; H, 6.02; N, 16.87. Found: C, 38.25; H, 5.91; N, 16.82.

Synthesis of 1,3,5,7-Tetracarbomethoxy-1,3,5,7-tetraazaheptane (V).

Methanedi(methylcarbamate), III (0.81 g., 0.005 mole), paraformaldehyde (0.08 g., 0.0025 mole) and toluenesulfonic acid (0.017 g.) were refluxed in methylene chloride (20 ml.) for 15 minutes. Then this was stirred at room temperature for 18 hours. More solvent (chloroform, 100 ml.) was added. The solution was washed with dilute NaOH solution, salt water and dried (sodium sulfate). Removal of solvent gave a colorless viscous oil (crude wt. 0.88 g.). This oil showed two spots and a short tailing from the base line on a silica gel tlc plate (benzene:acetone 4:1), one corresponding to starting material (minor) and a new product (major). This oil was dissolved in chloroform (10 ml.) and chromatographed through a silica gel column (53 x 2.0 cm). The column was eluted with benzene:acetone 4:1. First 2 x 100 ml. of the eluent gave the starting material. The latter fractions gave the product V as an oil which was triturated with methanol-petroleum ether (30-60°) to give a white crystalline solid. This was recrystallized from acetone-petroleum ether (30-60°), m.p. 139-140°, yield 0.58 g. (67%); nmr (deuteriochloroform): 3.68 δ (s, 6H), 3.78 δ (s, 6H), 4.70-4.88 δ (d, 4H), 5.03 δ (s, 1H), 5.70-6.15 δ (broad, 2H). On adding deuterium oxide, the broad peak at 5.70-6.15 δ disappeared and the doublet at 4.70-4.88 δ collapsed to a singlet; ir (potassium bromide): 1720, 1690 cm^{-1} (>C=O); MS: molecular ion peak at m/e 336.

Anal. Calcd. for $C_{11}H_{20}N_4O_8$: C, 39.29; H, 5.95; N, 16.66. Found: C, 39.28; H, 6.19; N, 16.48.

Cyclization of 1,3,5,7-Tetracarbomethoxy-1,3,5,7-tetraazaheptane (V) to Tetrazocine Derivative (II).

1,3,5,7-Tetracarbomethoxy-1,3,5,7-tetraazaheptane (0.336 g., 0.001 mole), paraformaldehyde (0.032 g.) and *p*-toluenesulfonic acid (0.005 g.) were refluxed in carbon tetrachloride (4 ml.) for 5 hours. Chloroform (50 ml.) was added. The solution was washed with dilute sodium hydroxide solution, sodium chloride solution and dried (sodium sulfate). Removal of solvent gave a viscous oil, 0.35 g. Tlc indicated this to be a mixture of three components, possibly the triazine derivative (minor), the tetrazocine derivative (major) and some polymer which did not move from the base line. There were separated by chromatography over a silica gel column (30 x 1.5 cms). The column was eluted with benzene:acetone 4:1 to give a 30% yield (105 mg.) of triazine derivative and 45% yield (158 mg.) of the tetrazocine derivative. These were identified by comparison with authentic samples.

Polymethylene diurethanes were synthesized by reacting cathyl

chloride with corresponding polymethylene diamine utilizing a procedure similar to that of Rabjohn for preparing ethyl hydrazodicarboxylate (9).

Cyclization of Polymethylene Diurethanes with Paraformaldehyde in Refluxing Carbon Tetrachloride Using *p*-Toluenesulfonic Acid as a Catalyst.

The polymethylene diurethane (0.01 mole), paraformaldehyde (0.32 g., ~ 0.1 mole) and *p*-toluenesulfonic acid (0.034 g.) were refluxed in carbon tetrachloride (40 ml.) for 5 hours. More solvent (chloroform, 100 ml.) was added. The solution was washed with 5% sodium hydroxide solution, salt water and dried (sodium sulfate). Removal of solvent gave a colorless liquid. Products 1, 2 and 3 of Table II were distilled under reduced pressure. The results are listed in Table II.

Reaction of Methanedi(methylcarbamate) with Paraformaldehyde in Refluxing Carbon Tetrachloride Using *p*-Toluenesulfonic Acid as Catalyst.

Methanedi(methylcarbamate), III (0.81 g., 0.005 mole), paraformaldehyde (0.16 g. and *p*-toluenesulfonic acid (0.025 g.) were refluxed in carbon tetrachloride (20 ml.) for 5 hours. More solvent (chloroform, 80 ml.) was added. The solution was washed with dil. NaOH solution, salt water and dried (sodium sulfate). The solvent was removed to give a colorless viscous oil, 0.90 g. This showed a little tailing from the baseline and two distinct spots (one corresponding to triazine derivatives) on tlc. This oil was separated by chromatography over a silica gel column (40 x 1.5 cms). When the column was eluted with benzene:acetone 4:1, the triazine derivatives came first followed by the tetrazocine derivative. The tetrazocine derivative was obtained as an oil, 0.40 g. (46%). Supporting elemental analysis and spectral data are listed in Table III.

Reaction of Methanediurethane and Paraformaldehyde in the Presence of *p*-Toluenesulfonic Acid in Refluxing Chloroform.

Methanediurethane (0.95 g., 0.005 mole), paraformaldehyde, (0.16 g., 0.005 mole) and *p*-toluenesulfonic acid (0.025 g.) were refluxed in chloroform (20 ml.) for 5 hours. More chloroform (80 ml.) was added. The solution was washed with 5% sodium hydroxide solution, salt water and dried (sodium sulfate). Removal of solvent gave a colorless viscous oil. This showed two spots on tlc, one corresponding to triazine derivative and a new product. This oil was triturated with ether-petroleum ether (30-60°) mixture to give a white solid, 0.43 g., m.p. 102-103° (triazine derivative). The mother liquor was chromatographed over a silica gel column (45 x 1.5). The column was eluted with benzene:acetone 4:1. The remaining triazine derivative (0.15 g.) came out first followed by the tetrazocine derivative (0.30 g., 30%). The tetrazocine derivative is a viscous oil and could not be solidified. The elemental analysis and spectal data are described in Table III.

Thermal Stability of Tetrazocine Derivatives.

1,3,5,7-Tetracarbethoxyoctahydrotetrazocine (0.404 g.) was refluxed in carbon tetrachloride (5 ml.) for 10 hours. The solvent was removed to give a colorless oil. The tetrazocine derivative was found to be unchanged by comparison with starting material. This colorless viscous oil was distilled under reduced pressure using a short path distillation apparatus; b.p. 165-155°/0.01 mm (uncorrected, oil bath temperature was 200-205°) without any decomposition.

Conversion of 1,3,5,7-Tetracarbethoxyoctahydrotetrazocine to 1,3,5-Tricarbethoxyhexahydro-*s*-triazine.

1,3,5,7-Tetracarbethoxyoctahydrotetrazocine (0.404 g.) and *p*-toluenesulfonic acid (0.010 g.) were refluxed in carbon tetrachloride (8 ml.) for 10 hours. More solvent (chloroform, 40 ml.) was added. The solution was washed with 5% sodium hydroxide solution, salt water and dried (sodium sulfate). Removal of solvent gave a white solid which was recrystallized from ether-petroleum ether (30-60°), 0.340 g. (84%), m.p. 102-103°. This was found to be the 1,3,5-tricarbethoxyhexahydro-*s*-triazine by comparison with an authentic sample.

Conversion of 1,3,5-Tricarbalkoxyhexahydro-*s*-triazines to Tetrazocine Derivatives.

The triazine derivative (0.5 g.) was added slowly to well-stirred concentrated sulfuric acid (4 ml.) over a period of 5 minutes at room temperature (~ 21°). No rise in temperature was observed. The reaction mixture was stirred for 20 minutes and then poured on to ice water (200 ml.). The solution was neutralized with solid potassium carbonate and extracted with chloroform (150 ml.). The chloroform solution was dried (sodium sulfate) and solvent was removed to give a colorless viscous oil. This showed a single spot on tlc and identified to be the tetrazocine derivative (II). Tetrazocine derivatives thus obtained are listed in Table III.

Acknowledgement.

This work was supported by a grant from the Army Research Office, Durham, North Carolina, under Grant No. DAAA21-72-C-0477.

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* Present address of senior author: University of Texas at San Antonio, 4242 Piedies Drive East, San Antonio, Texas 78285.