A review article[12] on the methylation of lactams with diazomethane suggests that there is an intimate relationship between the position of the amide band and the orientation of methylation. Three major regions have been cited: (1) 1620–1680 cm^{-1}, O-methylation; (2) 1680–1720, O- and N-methylation with kinetic dependence; and (3) 1730–1800, N-methylation. The factual data in Table I indicates that such a correlation for uracil and its methyl derivatives is untenable. Also as illustrated in Table I, there is no apparent relationship between the acidic pK_a of uracil and the methyl derivatives and the yields or N:O ratios of the diazomethane reactions.

Experimental Section

Instrumentation and conditions for tlc and glpc analyses have been described in details in a related paper.[13] Melting points are uncorrected and microanalyses were performed by M-H-W Laboratories, Garden City, Mich. 48135.

Reaction of Uracil and Its Methyl Derivatives with Diazomethane.—To a mixture of 0.1 mmol of each of the pyrimidines **1**, **1a**, **6**, **7**, **8**, and **9** in 1 ml of anhydrous methanol was added 30 ml (3.5 mmol) of ethereal diazomethane. The solution was allowed to stir overnight when practically all the solid material had dissolved. Longer reaction time (48 hr) was allowed for uracil (**1**) when dimethylformamide instead of methanol was used. The solution was filtered, concentrated, and diluted to 1 ml volumetrically with methanol. Quantitative analyses by glpc for the four dimethyluracils were done by comparing their peak areas with those of the authentic samples on a 6 ft × 0.125 in. column packed with 10% Carbowax 20M on Anakrom ABS 60–70 mesh at the following conditions [T_I, T_C, T_D (°C)]: **2**, 250, 170, 260; **3**, 200, 120, 260; **4**, 250, 200, 260; and **5**, 200, 100, 260, and 30 cc/min of nitrogen. A homogeneous chromatogram was observed under the highest temperatures for all the dimethyluracil standard solutions [0.5 wt % in methanol and relative retention times (min) for **2**, **3**, **4**, and **5** are 10.0, 2.5, 18.0, and 1.0, respectively], except **4** showed a 7% rearrangement to **2**, and the yield of the latter in a methylation reaction was corrected accordingly. Under the various combination temperatures cited above, the methoxypyrimidones **8** and **9** were either retained or decomposed on the column. At the high temperature end, minor peaks identifiable as *N*-methyl- and dimethyluracils were seen whose areas accounted for <1% of the methoxypyrimidone injected.[14] The glpc properties of the methylthymines resemble those of the corresponding uracils and were analyzed in a similar manner. The results of the diazomethane reactions are summarized in Table I.

2-Methoxy-3-methyl-4-pyrimidone (3).—A mixture of 0.2 g (1.6 mmol) of 2-methoxy-4-pyrimidone (**8**)[13] in 5 ml of methanol was stirred with 30 ml (3.5 mmol) of ethereal diazomethane until the evolution of nitrogen had ceased. The solution was concentrated and chromatographed on a 9-g silica gel column with 25% ethyl acetate in chloroform as eluents, yielding 0.12 g (54%) of **3**. Recrystallization from anhydrous ether and sublimation (50°, 20 mm) gave a pure sample: mp 93–95°; uv $\lambda_{max}^{H_2O}$ 269 nm (ϵ 6130), 213 (4340) at pH 7.4; ir (KBr) 1635 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.42 (s, 3), 4.03 (s, 3), 6.17 (d, 1, J = 6 Hz), and 7.65 (d, 1, J = 6 Hz).

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.31; H, 5.81; N, 20.20.

3,5-Dimethyl-2-methoxy-4-pyrimidone (3a).—A mixture of 0.35 g (2.5 mmol) of 2-methoxy-5-methyl-4-pyrimidone[13] in 5 ml of methanol and 60 ml (7 mmol) of ethereal diazomethane was allowed to react, and the product was isolated as described for the preparation of **3**. Compound **3a**, 0.13 g (34%), was recrystallized from anhydrous ether and sublimed (50°, 20 mm): mp 106–108°; uv $\lambda_{max}^{H_2O}$ 272 nm (ϵ 6280), 217 (4630) at pH 7.4; ir (KBr) 1635 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.00 (d, 3, J = 1 Hz), 3.43 (s, 3), 4.00 (s, 3), 7.53 (q, 1, J = 1 Hz).

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.54; H, 6.74; N, 18.41.

Registry No.—**1**, 66-22-8; **1a**, 65-71-4; **3**, 27460-04-4; **3a**, 27460-05-5; **6**, 608-34-4; **7**, 615-77-0; **8**, 25902-86-7; **9**, 18002-25-0; diazomethane, 334-88-3.

(12) R. Gompper, *Advan. Heterocycl. Chem.*, **2**, 245 (1962).

(13) Part I: J. L. Wong and D. S. Fuchs, *J. Org. Chem.*, **35**, 3786 (1970).

(14) Pyrolysis of 4-methoxy-2-pyrimidone (**9**), 2 mg at 210–220° for 40 min in an evacuated tube, caused complete conversion to the following products identified by glpc and tlc: **1**, **2**, **4**, **5**, **6**, and **7**. Similar treatment of the 2-methoxy analog **8** yielded all of the above products plus **3**. In both cases, uracil (**1**) and the *N*-methyluracils **6** and **7** were the major products. For a reference to thermal-induced methyl migration of monomethoxypyrimidines, see D. J. Brown and T. C. Lee, *J. Chem. Soc. C*, 214 (1970), and refer to ref 13 for thermal and catalyzed isomerization of 2,4-dialkoxypyrimidines.

Evaluation of Acyloxysilane as an Acylating Agent for Peptide Synthesis

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Received August 17, 1970

Few synthetic reactions have received more attention in recent years than that of the formation of the peptide linkage.[1] Many newer methods involving the use of ingeniously designed coupling reagents have been discovered.[2-4] Recently, in our laboratory, we found that[5] silicon tetrachloride can act as a simple and efficient coupling reagent for the formation of amide from carboxylic acid and amine according to eq 1. Be-

$$2RCO_2H + 2R'NH_2 + SiCl_4 \xrightarrow{\text{pyridine}} 2RCONHR' + (SiO_2)_n + 4HCl \quad (1)$$

cause of the ready availability of silicon tetrachloride and its apparent efficacy in mediating the formation of the amide bond, we have extended our investigation to the use of silicon tetrachloride as a coupling reagent for peptide synthesis.

Preliminary experiments indicated that the condensation between an N-protected amino acid and an amino ester with silicon tetrachloride did not yield the desired depeptide. While the N-protected amino acid could be recovered essentially quantitatively from the reaction mixture, the starting amino ester was converted into a polymeric material. Apparently, under the reaction conditions, a facile polymerization of the amino ester occurred. Similar observation was made by Birkofer[6] who found that polyglycine was obtained from the reaction of ethyl glycinate with silicon tetrachloride (reaction 2). Our task was therefore to minimize this side reaction.

$$n\text{-}NH_2CH_2CO_2C_2H_5 + (n/4)SiCl_4 \longrightarrow (\text{—}NHCH_2CO\text{—})_n + (n/4)Si(OC_2H_5)_4 \quad (2)$$

Results

Preliminary Studies.—Pertinent to the problem at hand are the following observations. Trimethylace-

(1) For a summary of reagents for peptide formation, see M. Bodanszky and M. A. Ondetti, "Peptide Synthesis," Interscience, New York, N. Y., 1966.

(2) B. Belleau and G. Malek, *J. Amer. Chem. Soc.*, **90**, 1651 (1968).

(3) T. Mukaiyama, M. Veki, R. Matsueda, and H. Maruyama, *ibid.*, **91**, 1554 (1969).

(4) G. Gawne, G. W. Kenner, and R. C. Sheppard, *ibid.*, **91**, 5669 (1969).

(5) T. H. Chan and L. T. L. Wong, *J. Org. Chem.*, **34**, 2766 (1969).

(6) L. Birkofer and A. Ritter, *Justus Liebigs Ann. Chem.*, **612**, 22 (1958).

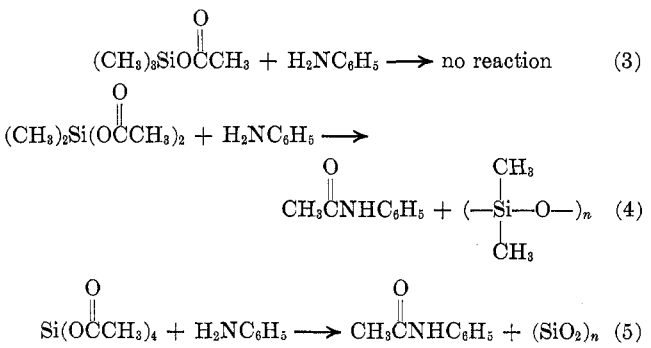
TABLE I

PREPARATION OF DIPEPTIDES BY SILICON TETRACHLORIDE

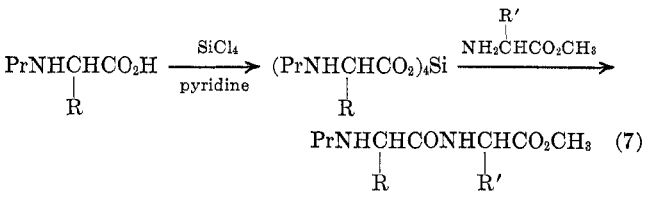
Acid	Amine	Registry no.	Dipeptide	Conditions of tetraacyloxysilane formation	Yield, %
Phth-gly	L-leu-OMe	27462-45-9	Phth-gly-leu-OMe[a]	110°, pyridine, 30 min	48
Phth-gly	gly-OEt	2641-02-3	Phth-gly-gly-OEt	110°, pyridine, 30 min	45
Phth-DL-ala	DL-ala-OEt	27519-54-6	Phth-DL-ala-DL-ala-OEt	110°, pyridine, 2 hr	51
Bz-DL-ala	DL-ala-OEt	27462-46-0	Bz-DL-ala-DL-ala-OEt	110°, pyridine, 1 hr	58
Bz-L-leu	gly-OEt	4905-35-5	Bz-leu-gly-OEt[b]	110°, pyridine, 45 min	65
Bz-L-leu	gly-OEt		Bz-leu-gly-OEt[b]	Na salt, acetonitrile–benzene	62
Ac-DL-phe	DL-ala-OEt	27462-48-2	Ac-DL-phe-DL-ala-OEt	110°, pyridine, 1 hr	60
Ac-L-phe	L-ala-OMe	27462-49-3	Ac-phe-ala-OMe[c]	110°, pyridine, 1 hr	43
Z-gly	gly-OEt	3005-87-6	Z-gly-gly-OEt	60°, pyridine, 1.25 hr	70
Z-gly	DL-ala-OEt	4066-23-3	Z-gly-DL-ala-OEt	60°, pyridine, 1.25 hr	54
Z-DL-ala	gly-OEt	4905-31-1	Z-DL-ala-gly-OEt	60°, pyridine, 1.25 hr	15

[a] $[\alpha]^{20}D$ +5.9° (*c* 3.6, $CHCl_3$). [b] Completely racemic product was obtained. [c] 40% DL isomer according to nmr.

toxysilane was found not to react with aniline to any significant extent, whereas dimethyldiacetoxysilane, under identical conditions (reflux benzene), reacted with aniline to give acetanilide in moderate yield (reaction 4). Tetraacetoxysilane reacted exothermically at room temperature with aniline to give acetanilide in excellent yield (reaction 5). This observation is contrary to that of Mehrotra[7] who reported that the reaction of acyloxysilane with aniline was substitution to give anilinosilane. While the origin of this difference is not clear to us, our observation does suggest that tetraacyloxysilane is a reasonable intermediate in the amide formation process (reaction 6). The first step of this pathway, substitution of chloro group by acyloxy group at silicon, is well documented.[8] Furthermore, it may be concluded that the amines can be added subsequently to the formation of the tetraacyloxysilane, and therefore the problem of polymerization of the amino ester (reaction 2) can be circumvented in this way.



Dipeptide Synthesis.—Appropriately N-protected amino acids were converted to their tetraacyloxysilanes by either (1) heating 4 mol of the amino acid with 1 mol of silicon tetrachloride in pyridine for 30 min to 2 hr, or (2) refluxing 4 mol of the sodium salt of the amino acid with 1 mol of silicon tetrachloride in acetonitrile–benzene mixture for 2 hr. The resultant tetraacyloxysilane was not isolated and was allowed to react *in situ* immediately. To the reaction mixture, the amino ester was added and the mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo* and the residue was decomposed with water. The organic material was extracted with ethyl acetate. The ethyl acetate solution, after washing with aqueous acid and alkaline solution, was evaporated to yield the crystalline dipeptide. The yields were moderate (Table I); however, there was no effort to optimize the conditions. In this way, a number of phthaloyl- (Phth), benzoyl- (Bz), and acetyl- (Ac) amino acids were condensed with various methyl or ethyl amino esters (reaction 7). The use of benzyloxycarbonyl (Z) as N-protecting group offered considerable difficulties. While Z-gly reacted with amino esters to give the corresponding dipeptides in reasonable yields, other Z-amino acids (*e.g.*, Z-ala, Z-leu) gave only poor yield of dipeptides. Further investigations showed that in the condensation of Z-ala with silicon tetrachloride extensive cleavage of the protecting group took place. One identifiable product was found to be tetrabenzyloxysilane (60% yield based on Z-ala). While the mode of formation of this compound is far from clear, it is likely that Z-amino acids upon heating decompose to give the Leuchs' anhydride and benzyl alcohol,[9] and the latter compound is known to react with silicon tetrachloride to give tetrabenzyloxysilane.[10]



Racemization Studies.—The extent of racemization during peptide synthesis by this method has also been examined. Recently, Halpern, *et al.*, proposed[11] the use of nmr method for the detection of racemization in the coupling of Ac-L-phe with L-ala-OMe. The chemical shifts of the CMe and the OMe are different for the LL and the DL diastereomers. The relative intensities of the nmr signals therefore reflect the degree of racemization. Using this method, the Ac-phe-L-ala-OMe obtained in Table I was found to contain 40 ± 2% of the DL diastereomer. This may be compared with the 50% DL in the product by using dicyclohexylcarbodiimide as the coupling reagent to a low 6% for the Woodward's reagent K.[11]

(7) R. C. Mehrotra, *Pure Appl. Chem.*, **13**, 111 (1966).
(8) A. G. Brook, *J. Amer. Chem. Soc.*, **77**, 4827 (1955).
(9) See J. P. Greenstein and M. Winitz, "The Chemistry of the Amino Acids," Vol. 2, Wiley, New York, N. Y., 1961, p 862.
(10) I. Joffe and H. W. Post, *J. Org. Chem.*, **14**, 421 (1949).
(11) B. Halpern, L. Chew, and B. Weinstein, *J. Amer. Chem. Soc.*, **89**, 5051 (1967).

Using the supersensitive Young's test,[12] the present method of peptide synthesis gave essentially racemic Bz-leu-gly-OEt, $[\alpha]^{20}D < 1°$. This, in comparison with other coupling methods (Table II) places the present

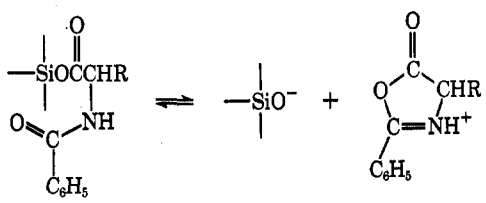
TABLE II
RACEMIZATION STUDIES BY YOUNG'S TEST

Bz-L-leu + gly-OEt ⟶ Bz-leu-gly-OEt

Method	$[\alpha]D$	L isomer, %, in excess of D isomer
Dicyclohexylcarbodiimide (NEt_3)	−5.5	16
N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline	−33.5	99[a]
Phenylisoxazolium (NEt_3), MeCN	−32.8	96
Silicon tetrachloride	<−0.4	1
Phosphorus trichloride	−0.6	2

[a] Reference 2, a result also confirmed by us.

method in an untenable position. The extensive racemization cannot be due to the presence of pyridine because, using the sodium salt of Bz-L-leu for the preparation of tetraacyloxysilane in acetonitrile–benzene, a racemic compound was also obtained. The mode of racemization is most likely due to the intervention of azalactone as an intermediate. We were indeed able to isolate 4-isobutyl-2-phenyloxazolone from the reaction mixture prior to the addition of gly-OEt. The oxazolone was found to be optically inactive. The following equilibrium may serve as the racemization mechanism.



Conclusion

The data presented in this work allows us to conclude that, while the present method can be used for peptide synthesis, the fact that the Z-protecting group shows instability under the reaction conditions and also the extensive degree of racemization during peptide synthesis renders this method not a valuable one. It may offer some advantages in the coupling of phthaloylamino acids in that silicon tetrachloride is relatively inexpensive and the reaction is generally clean and free of contamination with side products.

Experimental Section[13]

Reaction of Aniline with Acetoxysilanes. A. Trimethylacetoxysilane.—To 5 g of trimethylacetoxysilane in 20 ml of benzene was added 7.2 g of aniline. The solvent was refluxed for 3 hr and then fractionated to give back 4.5 g of acetoxysilane, 6.6 g of aniline, and a residue containing <0.5 g of acetanilide (5% based on aniline used), mp 110–112°.

B. Dimethyldiacetoxysilane.—To 3.4 g of dimethyldiacetoxysilane in 20 ml of benzene was added 3.6 g of aniline. The solution was refluxed for 2 hr. The solvent was evaporated and the residue was hydrolyzed with water and extracted with ethyl acetate. The extract, after washing with diluted acid and base, gave on evaporation 1.4 g (54%) of acetanilide.

C. Tetraacetoxysilane.—To a solution of 2.0 g of tetraacetoxysilane[14] in 20 ml of dry pyridine, 1.4 g of aniline was added slowly. The solution was left stirring overnight at room temperature. It was poured into ice–water and the aqueous filtrate was evaporated to give, on recrystallization, 1.7 g (84%) of acetanilide.

Examples of Dipeptide Synthesis. Phthaloylglycylglycine Ethyl Ester.—To a solution of 2.43 g of phthaloylglycine in 20 ml of pyridine, a solution of 0.5 g of silicon tetrachloride in 5 ml of benzene was added slowly with stirring. The mixture was heated at 110° for 30 min. To the cooled mixture, 0.61 g of ethyl glycinate was added and the mixture was stirred overnight at room temperature. The mixture was then evaporated under vacuum at 50° and the residue was hydrolyzed with water and extracted with ethyl acetate. The organic phase was washed with dilute hydrochloric acid, water, dilute sodium bicarbonate solution, and then water, The organic solution was dried and evaporated to give 0.76 g (45%) of product which on recrystallization from ethyl acetate–*n*-hexane gave a colorless solid, mp 193–195° (lit. mp 194–195°).

Acetyl-DL-phenylalanyl-DL-alanine Ethyl Ester.—To a solution of 2.5 g of acetyl-DL-phenylalanine in 20 ml of pyridine was added 0.5 g of silicon tetrachloride in 5 ml of benzene. The mixture was heated at 110° for 1 hr and cooled to room temperature. DL-Alanine ethyl ester (0.70 g) was added and the mixture was left stirring overnight. On working up, the mixture gave 1.1 g (60%) of acetyl-DL-phenylalanyl-DL-alanine ethyl ester, mp 186–188°.

Benzyloxycarbonylglycyl-DL-alanine Ethyl Ester.—To a solution of 2.5 g of benzyloxycarbonylglycine in 20 ml of pyridine heated at 60° was added 0.5 g of silicon tetrachloride in 10 ml of benzene over 40 min. The mixture was kept at about 60° for 0.5 hr and then cooled to room temperature. DL-Alanine ethyl ester (0.70 g) was added and the mixture was stirred overnight. On working up, the mixture gave 1.0 g of product, mp 52–54° (lit. mp 53–55°).

Isolation of Tetrabenzyloxysilane from the Reaction of Benzyloxycarbonylalanine with Silicon Tetrachloride.—To a solution of 1.32 g of benzyloxycarbonyl-DL-alanine in 10 ml of pyridine was added 0.25 g of silicon tetrachloride and the mixture heated at 110° for 2 hr. After cooling, the pyridine was distilled and the residue was chromatographed on column (silica gel) with benzene. The first product collected was identified by comparison with authentic sample to be tetrabenzyloxysilane (0.41 g, 60%).

Racemization Studies. A. Nmr Method, Acetylphenylalanylalanine Methyl Ester.—To a solution of 2.5 g of acetyl-L-phenylalanine in 20 ml of pyridine was added 0.5 g of silicon tetrachloride in 10 ml of benzene. The mixture was heated at 110° for 1 hr and cooled to room temperature. L-Alanine methyl ester hydrochloride (0.83 g) was added to the mixture and this was followed by 0.60 g of triethylamine. The mixture was left overnight. After the pyridine was removed *in vacuo*, the residue was hydrolyzed with a little water and extracted with ethyl acetate. The organic phase, after washing with dilute acid and base, was dried and evaporated to give 0.75 g of solid residue. Its nmr spectrum ($CDCl_3$) showed the methyl resonance as two overlapping doublets at 81 and 73 Hz downfield from TMS and relative intensities of 60:40.

B. Young's test. Benzoylleucylglycine Ethyl Ester.—To a solution of benzoyl-L-leucine (2.61 g) in 20 ml of pyridine, was added 0.47 g of silicon tetrachloride in 5 ml of ether. The mixture was heated at 100° for 45 min and cooled to room temperature. A solution of 0.575 g of ethyl glycinate in 1 ml of ether was added and the solution was stirred overnight. The mixture on working up gave 1.16 g of white solid, mp 137–145°, $[\alpha]^{17}D$ −0.5° (*c* 3.01, ethanol).

C. Isolation of 4-Isobutyl-2-phenyloxazolone.—To a solution of 2.78 g of benzoyl-L-leucine in 30 ml of acetonitrile was added 0.58 g of sodium hydride (53.7% in paraffin). The mixture was stirred for 1 hr. To the mixture was added 20 ml of acetonitrile and 15 ml of benzene and then 0.5 g of silicon tetrachloride in 5 ml of benzene. The mixture was heated at reflux for 2 hr and cooled to room temperature. The solvent was evaporated *in vacuo* to give a residue which was triturated with *n*-hexane. The hexane solution on evaporation gave a crystalline solid, mp 40–45°. It weighed 0.29 g (11%) and showed in ir (Nujol) ν_{max} at 1830

(12) M. Williams and G. Young, *J. Chem. Soc.*, 881 (1963).
(13) Melting points are not corrected.
(14) S. Dandegaonker, *J. Karnatak Univ.*, **7**, 95 (1964).

and 1665 cm^{-1}. It showed no optical activity, $[\alpha]^{18}D$ 0° (*c* 2.0, ethanol).

Registry No.—Silicon tetrachloride, 10026-04-7; trimethylacetoxysilane, 2754-27-0; dimethyldiacetoxysilane, 2182-66-3; tetraacetoxysilane, 562-90-3; 4-isobutyl-2-phenyloxazolone, 27460-46-4.

Some Observations on the Mechanism of a Modified Knorr Pyrrole Condensation[1a]

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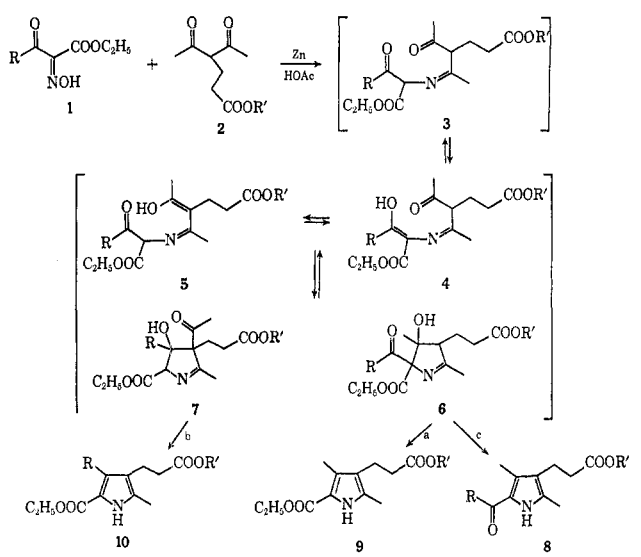
In preparing some pyrrolic intermediates for porphyrin synthesis *via* a modified Knorr condensation, contamination of the pyrrole by initially unidentified side products led us to a study of the effect of the structure of the β-keto ester on the mechanism of this reaction. It seemed conceivable that, in light of Scheme I, three

SCHEME I



pyrrolic products (**8**, **9**, and **10**) could be obtained. The postition of equilibrium between enols **4** and **5** and the relative rates of nucleophilic attack on the acyl groups of **6** and **7** are the factors which must be considered in deciding which pyrrole will predominate.

An earlier investigation of this condensation[2] showed that, when ethyl 4-acetyl-5-oxohexanoate (**2**, R′ = C_2H_5) was condensed with the oximino derivative of diethyl 3-oxoglutarate (**1**, R = CH_2COOEt), pyrrole **9** (R′ = C_2H_5) was isolated in 16.5% yield. Also, 3-methyl-2,4-pentanedione condensed with diethyl 2-oximino-3-oxoadipate (**1**, R = CH_2CH_2COOEt) to give 40% of the analogous structure, 2-carbethoxy-3,4,5-trimethylpyrrole. Since such a large percentage of starting materials remained unaccounted for, participation of path b was still a very real possibility, hence our investigation of the problem.

All of our condensations were carried out under standardized conditions (not optimized for maximum yields), and used the same β-diketone, namely, methyl 4-acetyl-5-oxohexanoate (**2**, R′ = CH_3); only the β-keto ester was varied. Ethyl acetoacetate-3-^{14}C, our first choice, afforded several advantages. First, there are no steric or electronic differences between the acyl groups that must be lost from **6** and **7**. Second, both **9** and **10** become structurally identical, eliminating any separation problem. Third, the fact that **10** is radioactively labeled permits a quantitative determination of the two potential pathways.

Labeled acetoacetic esters were converted to their oximino derivatives and condensed with an equimolar amount of **2** (R′ = CH_3). The pyrroles were isolated and purified, and their specific activities were compared to those of the starting β-keto esters. The results obtained in two experiments with the ethyl ester and one with the benzyl ester indicate that a is the major pathway for pyrrole formation (Table I).

TABLE I
CONDENSATION OF METHYL 4-ACETYL-5-OXOHEXANOATE (2) AND LABELED 2-OXIMINO-β-KETO ESTERS

β-Keto ester	Specific activity, dpm/mm, β-keto ester	Specific activity, dpm/mm, pyrrole	% path b	% yield of pyrrole (9 + 10)
Ethyl 2-oximinoacetoacetate-3-^{14}C, expt 1	39,960	470	1.2	45
Ethyl 2-oximinoacetoacetate-3-^{14}C, expt 2	27,890	440	1.6	37
Benzyl 2-oximinoacetoacetate-3-^{14}C	51,370	640	1.2	34

The mother liquors from the condensation with benzyl acetoacetate were then inspected for evidence of the presence of pyrrole **8** (R, R′ = CH_3) resulting from path c. Preparative tlc afforded a small amount of material identified as **8** by its uv absorption ($\lambda_{max}^{CH_3OH}$ 305 nm) and mass spectrum [*m/e* 223 (M^+, 56), 180 (5), 150 (100), 43 (48)], identical with an authentic sample prepared from 3,5-dimethyl-4-(β-carbomethoxyethyl)-2-carbethoxypyrrole by hydrolysis, decarboxylation, acetylation, and reesterification. However, its contribution was estimated to be much less than 1% of the total pyrrolic product.

The small contribution of path c in the reaction is understandable, since nucleophilic attack on **6** would prefer the more polar acetyl carbonyl. The difference between paths a and b is more complicated. In the enolic mechanism we have invoked, enol **4**, having the extended conjugation of the ester carbonyl, could be expected to predominate. In addition, molecular models show the acetyl group of **6** to present slightly less hindrance to attack. Both of these considerations favor path a, and this prediction is borne out experimentally.

Our next objective was to investigate the results of changing the steric and electronic situation by varying R in the starting β-keto ester. In this case, since two chemically different pyrroles were to be produced, evi-

(1) (a) Supported in part by Grant AI-04888 from the National Institutes of Health, U. S. Public Health Service; (b) National Institutes of Health Predoctoral Fellow.

(2) E. Bullock, A. W. Johnson, E. Markham, and K. B. Shaw, *J. Chem. Soc.*, 1430 (1958). In this paper it is recognized for the first time that use of a 3-alkyl-2,4-pentanedione, rather than acetylacetone itself, with the oximino-β-keto ester **1** causes the condensation to take a completely different course. The former gives a 2,4-dimethylpyrrole analogous to **9**, while the latter gives the normal Knorr product, 4-acetyl-2-carbethoxy-3,5-dimethylpyrrole.