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PEPTIDES FROM NON-AMINO ACID SOURCES III.
SYNTHESIS OF DIKETOPIPERAZINE DERIVATIVES FROM KETENE ACETAL.

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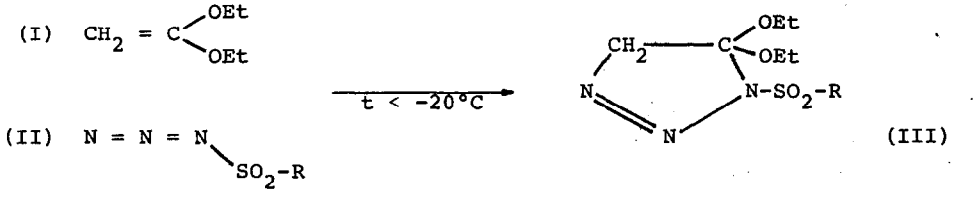
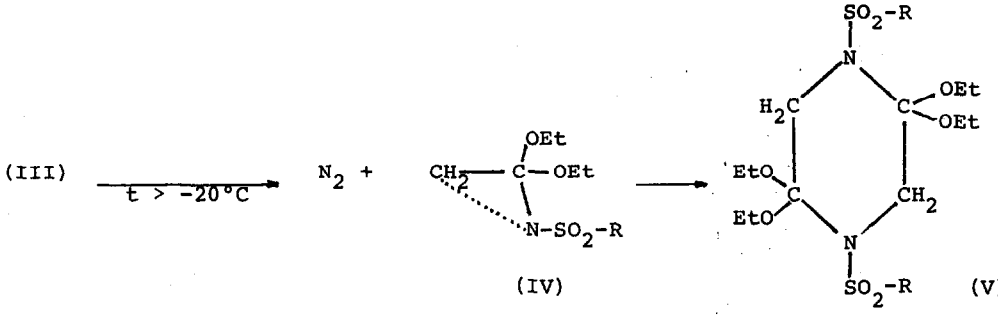
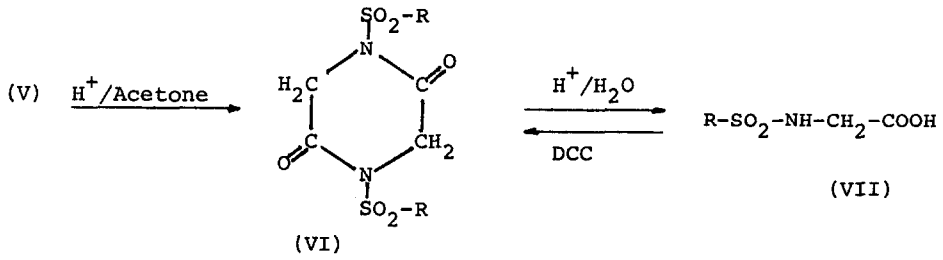
We wish to report a new synthetic route to N,N'-disubstituted diketopiperazines (VI) via their tetraethyl acetals (V) from ketene acetal (I) and sulfonic azides (II). Compounds I and II reacted completely within 24 hours at -20°C in a 1:1 molar ratio in the absence of a solvent. The yield was nearly quantitative with a small amount of ether soluble oily byproduct.







The ketene acetal (I) was prepared as described by Johnson et al (1) while the azides (R = CH_3 and C_6H_5 in II) were obtained according to the procedure of Horner et al (2). The characteristics of the products are summarized in Table I.

Spectroscopic evidence indicates that the reaction, analogously to that of similar systems (3), proceeds through a five membered ring intermediate (III). This triazine readily undergoes nitrogen extrusion which formally produces the corresponding aziridine. However, this aziridine could not be isolated or detected. Consequently it is believed that the highly reactive intermediate is better represented by structure (IV) which readily forms the corresponding diketopiperazine derivative (V). Since the two particular derivatives (R = CH_3 and C_6H_5 in V) have not been reported previously, in addition to spectroscopic evidence, their structure were established by degradation. Acid catalysed hydrolysis of the tetraethyl acetals (V) yielded N,N'-disubstituted diketopiperazines (VI) which were further hydrolysed to two moles of N protected glycines (VII). The physical characteristics of the hydrolysis products VI and VII were identical with those of the authentic samples prepared according to Berse et al (6) and McChesney et al (7), respectively.

Although it is known (8) that, depending on the reaction conditions, an activated aziridine may form both piperazine (dimer) and polymer in various proportions, in the present case no aziridine derivative has been detected as an intermediate. It is likely that the intermediate is formed with an "open-ring structure" analogously to episulfides (9) or to intermediate of the

addition of triplet nitrene to olefins (10). Quantum chemical investigation of this aspect of aziridine ring formation is in progress (11). It is hoped that the theoretical and experimental investigation now in progress may illuminate the way to the synthesis of polypeptides from non-amino acid sources (12, 13).

TABLE I

Physical Characteristics of Diketo Piperazine Derivatives*

	Compound V				Compound VI			
	R = $-CH_3$		R = $-C_6H_5$		R = $-CH_3$		R = $-C_6H_5$	
Mp (°C)	132-133		29-30		295-300		295	
I.R. $\tilde{\nu}$ (cm^{-1}) KBr pellet.**	3000	1040	1650	1060	1690	850	1695	780
	1330	1000	1250	750	1180	770	1255	730
	1180	775	1160	725	1125		1150	
	1160	750	1125	680	1000		1100	
	1120	650	1090		970			
	1100							
N.M.R. δ(ppm) in Pyridine	4.05	S 4H	4.65	S 4H	***		***	
	4.38	Q 8H	3.10	Q 8H				
	4.70	S 6H	0.90	T 6H				
	1.20	T 12H	0.50	T 6H				

* All new compounds gave satisfactory elemental analysis (CH, N and S).

** For compound V. (R = C_6H_5) the I.R. Spectrum was recorded in Nujol mull.

*** The limited solubility of these compounds in most solvents did not permit the recording of satisfactory N.M.R. Spectrum.

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3. The -N = N - N< group in the thiatriazole and tetrazolinethione rings exhibits an I.R. absorption maximum in the region of 1300 - 1270 cm^{-1} (4). In addition, we have found that the N-carbethoxy analogue of III showed a similar absorption at 1340 cm^{-1} which disappeared when the ring rearranged to the corresponding oxazolidine derivative (5). In the case of the addition of benzene sulfonic-azide (II) to ketene acetal (I) a characteristic I.R. frequency of 1420 cm^{-1} was found which may be considered as spectroscopic evidence for the existence of the corresponding triazole intermediate (III).

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