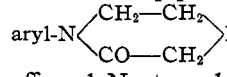
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF SWARTHMORE COLLEGE]

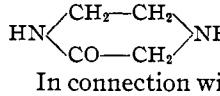
A Synthesis of Monoketopiperazines

BY SAMUEL R. ASPINALL

Monoketopiperazines of the type

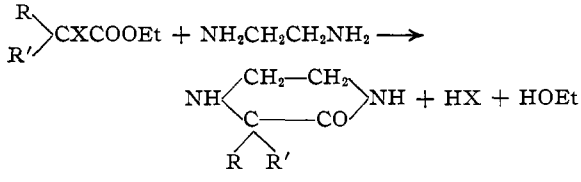


were prepared by Bischoff and Nastvogel in 1889[1] by condensing N,N′-diarylethylenediamines with chloroacetic acid in the presence of sodium acetate; and in 1892 Bischoff and Trapesonzjanz[2] prepared the same compounds by reducing 1,4-diaryl-2,3-diketopiperazines[3] using various metal-acid combinations. The 2,3-diketopiperazines had been obtained by heating N,N′-diarylethylenediamines with oxalic acid. No significant information in regard to yields is given in any of this work. No further synthetic work on monoketopiperazines has been carried out and the non-arylated type

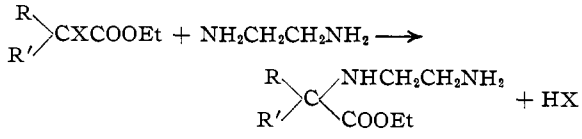


never has been reported.

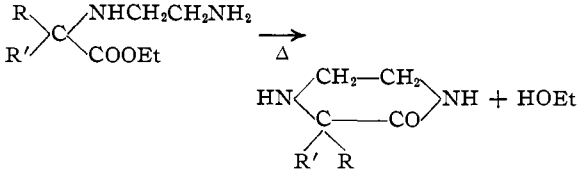
In connection with a more extended study of the interaction of ethylenediamine and various organic esters,[4] it has now been found that α-halogen esters react with ethylenediamine to give satisfactory yields of the non-arylated type of monoketopiperazines according to the following equation, where R and R′ may be alkyl or hydrogen.



That the first phase of the reaction is alkylation of the ethylenediamine is evidenced by the fact that when the two reactants are mixed there is a violent reaction with evolution of heat and the simultaneous liberation of ionic halogen. This is consistent with the usual behavior of aliphatic amines with α-halogen compounds; furthermore, it is generally true that an amidation at room temperature by means of an ester is not a fast, violent reaction. It is then obvious that the reaction should be carried out under conditions favorable to the formation of a monoalkylethylenediamine, as follows



This requires slow addition of the halogen ester to an excess of ethylenediamine diluted as much as feasible with some inert solvent. The liberated halogen acid, which is absorbed by the reaction mixture, is destroyed by sodium ethylate, the sodium halide so produced is filtered off and the solvent and excess ethylenediamine are removed by distillation at the water pump. When the residual monoalkylethylenediamine is heated at 200° under high vacuum, cyclization occurs and the monoketopiperazine distils over as a pale yellow oil. After solidification, it is obtained as a pure white, well-defined solid by recrystallization.



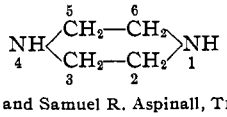
Experimental

The following description of the synthesis of 2-ketopiperazine is typical also of its 3-alkyl and 3,3,-dialkyl derivatives.

2-Ketopiperazine.—One-sixth of a mole (20.4 g.) of ethyl chloroacetate dissolved in 100 cc. of absolute alcohol is slowly added at room temperature to a well-stirred solution of one mole (60 g.) of anhydrous ethylenediamine in 300 cc. of absolute alcohol. The addition requires about three hours and the mixture is allowed to stand for an additional two hours. One-sixth of a mole (11.3 g.) of sodium ethylate in alcohol solution is added, the precipitated sodium chloride filtered off and the alcohol and excess ethylenediamine removed by distillation at the water pump. Upon heating the residual reaction mass at 200° under 5 mm. pressure, 2-ketopiperazine is formed and distils at about 165° (uncor.) as a pale yellow oil. After solidification, it is obtained as well-defined white crystals melting at 136° (cor.) by recrystallization from acetone–petroleum ether. The yield is 45% of the theoretical.

The effects of using other reaction temperatures, other concentrations of reactants and replacement

(1) Bischoff and Nastvogel, *Ber.*, **22**, 1783 (1889).
(2) Bischoff and Trapesonzjanz, *ibid.*, **25**, 2931 (1892).
(3) The piperazine ring is numbered as shown



(4) Arthur J. Hill and Samuel R. Aspinall, THIS JOURNAL, **61**, 822 (1939); Samuel R. Aspinall, *ibid.*, **61**, 3195 (1939).

TABLE I

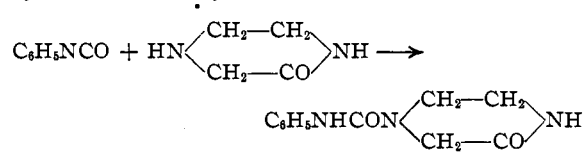
MONOKETOPIPERAZINES AND THEIR BENZENE SULFONAMIDES

Reacting ethyl ester	Product	M. p., °C. cor.	Yield, %	Recryst. solvent[a]	N, % Calcd.	N, % Kjeld.[b]	Benzenesulfonamide M. p., °C. cor.	Benzenesulfonamide N, % Calcd.	Benzenesulfonamide N, % Kjeld.[b]
α-Chloroacetate	$C_4H_8ON_2$	136	45	Acetone	28.00	28.15	188	11.67	11.69
α-Bromo-*n*-butyrate	$C_2H_5C_4H_7ON_2$	60	60	EtOAc	21.88	21.97	148	10.45	10.50
α-Bromo-isobutyrate	$(CH_3)_2C_4H_6ON_2$	134	40	EtOAc	21.88	21.89	206	10.45	10.54

[a] Precipitation of the ketopiperazines is more complete if petroleum ether is added to the solvent. [b] Reported analytical results are the averages of two determinations, neither of which differs from the calculated by more than 0.15% absolute error.

of chloroacetic ester by bromoacetic ester were studied. 1. Syntheses carried out at −15°, 0° and +80° gave the same yields as those at room temperature. 2. The extent to which ethylenediamine is present in excess profoundly affects the yield of end-product, because a large excess of ethylenediamine favors the monoalkylation essential to the eventual formation of monoketopiperazine. When one mole of ethylenediamine is treated with one mole of ethyl chloroacetate under the conditions described above, there is a quantitative precipitation of one-half mole of ethylenediamine dihydrochloride which is insoluble in the absolute alcohol medium. The remaining one-half mole of ethylenediamine was necessarily dialkylated and it is found that no monoketopiperazine is obtained. When one mole of ethylenediamine is treated with one-third mole of ethyl chloroacetate, there is no precipitation of ethylenediamine dihydrochloride (which is soluble in the alcohol–ethylenediamine medium) and the yield of monoketopiperazine is 25% of the theoretical. It is probable that the yield of monoketopiperazine could be increased to any desired amount if a sufficient excess of ethylenediamine were used. 3. The replacement of the chloroester by the bromoester has no effect on the yield, but has the disadvantage that the sodium bromide formed by the addition of sodium ethylate is soluble in the reaction mixture and special steps must be taken for its removal before a smooth distillation is possible. The method adopted was as follows. After addition of the bromoester in the usual way, the alcohol and most of the ethylenediamine were removed by distillation at the water pump and a dilute benzene solution of one equivalent of sodium ethylate was added. The sodium bromide, which is insoluble in benzene, was filtered off, the benzene and remaining ethylenediamine removed and the product distilled as before. 3-Ethyl-2-ketopiperazine and 3,3-dimethyl-2-ketopiperazine were prepared by this procedure from ethyl α-bromo-*n*-butyrate and ethyl α-bromo-isobutyrate, respectively.[5]

The ketopiperazines, which are extremely soluble in cold water and alcohol and insoluble in ether and petroleum ether, are best recrystallized from ethyl acetate or acetone, with or without the addition of petroleum ether. The compounds react strongly basic in water solution and give the usual diagnostic reactions of amines. For purposes of further characterization the ketopiperazines were converted to crystalline benzene sulfonamides by shaking an aqueous solution of 2.5 equivalents of the base with benzenesulfonyl chloride. The sulfonamides precipitated immediately with evolution of heat, and were recrystallized from water. Monoketopiperazine itself was more thoroughly characterized by preparing and analyzing the following derivatives. (1) The picrate was made in alcohol and recrystallized from water. (2) The hydrochloride was prepared by passing dry hydrogen chloride into an absolute alcohol solution of the base, and recrystallizing from absolute alcohol. It is extremely soluble in water. (3) The phenyl ureido derivative, which precipitated immediately with evolution of heat when an acetone solution of the base was treated with one equivalent of phenyl isocyanate, was recrystallized from absolute alcohol.



The phenyl thioureido derivative, similarly prepared from phenyl isothiocyanate, was recrystallized from 95% alcohol. Further investigation of this synthesis is in progress.

(5) The low solubility reported for potassium bromide in alcohol and alcohol–water mixtures indicates that potassium ethylate or even potassium hydroxide could be advantageously used to precipitate hydrogen bromide from the original reaction mixture without the use of benzene.

TABLE II
DERIVATIVES OF 2-KETOPIPERAZINE

	M. p., °C. cor.	N, % Calcd.	Kjeld.[a]
Picrate	180	21.28	21.19
Hydrochloride	208	20.51	20.65
Phenylurea	171	19.18	19.18
Phenylthiourea	199	17.87	17.85

[a] Reported analytical results are the averages of two determinations, neither of which differs from the calculated by more than 0.15% absolute error.

Summary

1. A practical synthesis for the hitherto unknown 2-ketopiperazine and its 3-alkyl and 3,3-dialkyl derivatives has been developed.

2. A study of the reaction between ethylenediamine and α-halogen esters under different conditions has been carried out.

3. The piperazines prepared in this study have been fully characterized by reaction with such typical amine reagents as benzenesulfonyl chloride, picric acid, hydrogen chloride, phenyl isocyanate and phenyl isothiocyanate.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE UNIVERSITY OF TEXAS]

The Relationship of Inositol, Thiamin, Biotin, Pantothenic Acid and Vitamin B_6 to the Growth of Yeasts

BY ROGER J. WILLIAMS, ROBERT E. EAKIN AND ESMOND E. SNELL

The specific chemical substances found to be effective constituents of culture media for promoting the growth of yeasts are of general biological interest. Inositol, found to be a growth factor for yeast in the laboratory of W. Lash Miller,[1] is of widespread occurrence in the tissues of plants and animals. Thiamin (vitamin B_1), first found to be effective for yeast in the author's laboratory,[2] was a recognized vitamin long before and has since proved to be of widespread significance in cellular physiology, functioning as the organic moiety of co-carboxylase (and perhaps in other ways). Biotin, discovered in the laboratories of F. Kögl,[3] is widely distributed and is physiologically effective for a number of organisms.[4,5,6] Pantothenic acid, discovered and concentrated in the author's laboratory,[7,8] is now recognized as identical to the filtrate factor or the chick antidermatitis vitamin,[9,10] and probably stimulates the growth of rats.[11] It is of ubiquitous occurrence and has been found essential for the growth of many bacteria[12,13] and to stimulate the growth of green plants[14] and the respiration of widely different tissues. It appears to be an essential constituent of some important enzyme systems.[15] β-Alanine is a component part of pantothenic acid[16] and may itself serve as a precursor of pantothenic acid both for yeasts and for certain bacteria.[13,16,17] Vitamin B_6 (adermin), recently found to be a growth factor for yeast,[18,19] bacteria,[20] and higher plants,[21] has for some time been recognized as a vitamin essential for rats.

Through the kindness of Professor Kögl, who has placed a sample of biotin at our disposal, we are now in a position to study the interaction of all of the factors enumerated above in promoting the growth of yeasts. The results of such studies may prove of great interest both from the standpoint of yeast physiology and because of the light which they may throw on the interplay of these

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