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1,3-BISPHENYLMALONDIAMIDINE. EXCLUSIVE C- OR N-METHYLATION OF ITS ANION.

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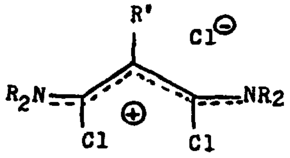
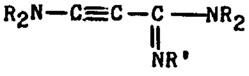
Various aza analogs of malonyl chemistry derive from phosgenimonium (PI) salts.1) The 1,3-dichlorotrimethine malonylcyanines (I)2), ynamines amidines (II)3), chloroenamine acid chlorides (III)4), and the β-lactam (IV)4) are typical examples.

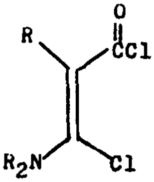


I

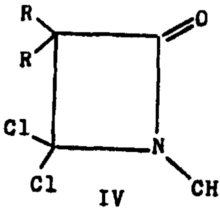


$R_2N{-}C{\equiv}C{-}\overset{\displaystyle C}{}\!\underset{NR'}{\overset{}{\|}}{-}NR_2$

II

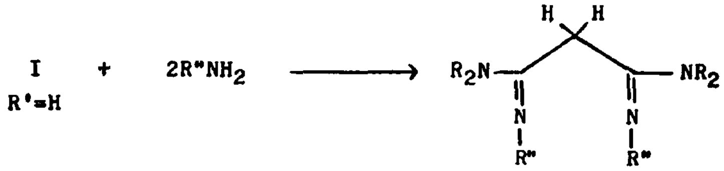


III



IV

Many useful products are obtained starting from the malonylcyanines (I), and particularly the malondiamidines (V) which result from the reaction of I with primary amines.2,5)

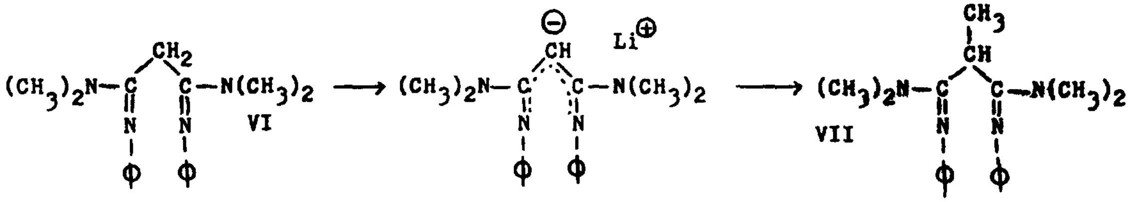


V

The malondiamidines (V), can be considered as the aza analogs of malonic esters, and while the alkylation reactions of malonic esters belong to classical chemistry6), the C- versus N-methylation of a malondiamidine is reported now.

The bisphenylmalondiamidine (VI)5) (V: R=Me, R'=ϕ) was prepared from the methylcyanine I (R=Me, R'=H) and aniline in 75% yield. The metalation of VI by methyllithium (MeLi) was accomplished in the following manner:

60ml of MeLi (0.2N) in ether were put, under nitrogen, into a three necked flask. At -78° a solution of 1.1g (3.3 mmoles) of VI in 60ml dry THF was introduced slowly by way of a syringe. The solution which was stirred magnetically was allowed to reach room temp. and after 2 hrs cooled to -40° and 1.7g of MeI were added. Stirring was then continued for 2 hrs and after the usual work up a liquid product, which was identified as the C-methyl derivative VII of VI, was obtained in 85% yield.



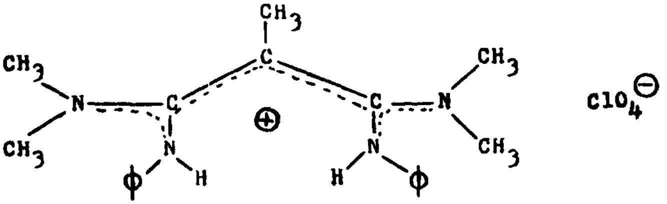
VII. NMR (δ, $CDCl_3$): 1.5/d(J=7.5), 3H(CH_3-C); 2.8/s, 12H(CH_3-N); 3.75/q(J=7.5), 1H($>C\underline{H}$-CH_3); 6.8-7.4/m, 10(aromatic). Irradiation at δ 3.75 resulted in the collapse of the doublet at δ 1.5 into a singlet. MS: M^+ 322 m/e and IR($CDCl_3$): 1605($>C=N-$).

In order to verify the structure of VII a sample of this compound was dissolved in ether, cooled to 0° and a few drops of $HClO_4$ were added followed by a few ml of EtOH. White crystals were formed which were filtered and washed with a little EtOH. The structure VIII was assigned for the new compound on the basis of its spectral properties. VIII was not soluble in $CHCl_3$ or CH_2Cl_2 and its solution in DMSO-d_6 gave the following NMR spectrum:

VIII. NMR (δ, DMSO-d_6): 1.75/s, 3H(CH_3-C); 2.62/s, 12H(CH_3-N); 6.6-7.4/m, 10H(aromatic). The two $\underline{H}$-N protons were exchanged by the solvent.

In the IR spectrum of VIII absorptions at 3265 cm^{-1} ($>NH$), 1050-1140 cm^{-1} ($ClO_4^{\ominus}$), and 1620 cm^{-1} ($C\overset{\cdots}{=}N$) were observed.

VIII

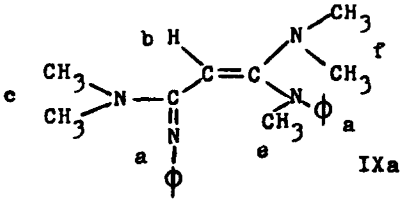


In order to perform the metalation of VI by $NaNH_2$, 100ml of liquid ammonia were introduced into a three necked flask and 300mg of sodium, followed by a crystal of $Fe(NO_3)_3$, were added to the liquid. After the formation of sodium amide was completed 1.0g (3.22 mmoles) of VI was added and the solution was stirred for 2.5 hrs and its color turned green when all of VI dissolved. 1ml of CH_3I in 50ml of ether were added and the ammonia was allowed to evaporate slowly. The ether solution was then poured into cold water, the layers separated and the organic layer was dried over $MgSO_4$. After filtration and the removal of the solvent the crude solid product was crystallized from pet. ether and had a m.p. of 101° (η=80%).

The substance, IX, had a complex NMR spectrum (T-60, $CDCl_3$) consisting of: aromatic multiplet between δ 7.2-6.4 and six singlets at δ 4.12, 3.1, 2.8, 2.79, 2.5, and 2.12. There was no change in the NMR spectrum following the addition of D_2O indicating the absence of an acidic hydrogen in IX. This conclusion was supported by the IR spectrum ($CHCl_3$) which contained no -NH absorption but revealed the presence of a conjugated -C=N- bond due to the absorption at 1610 cm^{-1}.

The MS of IX had M^+ of 322 m/e the same as for VII implying that both substances have the same molecular weight. It was shown that IX was not an iodine salt as Beilstein test performed on this compound gave a negative result.

Further NMR studies led us to the conclusion that IX was in fact a mixture of two geometric isomers resulting from N-methylation of the anion derived from VI in its reaction with NaNH$_2$/NH$_3$. The two isomers IXa (29%) and IXb (71%) showed the following NMR absorptions in two different solvents (δ, XL-100):



IXa

	CDCl$_3$	benzene-d$_6$
a 10H	6.5-7.4/m	6.5-7.4/m
b 1H	4.2/s	4.15/s
c 6H	3.07/s	2.75/s
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e 3H	2.8/s	2.64/s
f 6H	2.5/s	2.14/s
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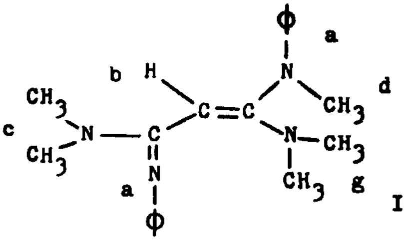

IXb

	CDCl$_3$	benzene-d$_6$
a 10H	6.5-7.4/m	6.5-7.4/m
b 1H	4.2/s	4.15/s
c 6H	3.07/s	2.91/s
d 3H	2.85/s	2.8/s
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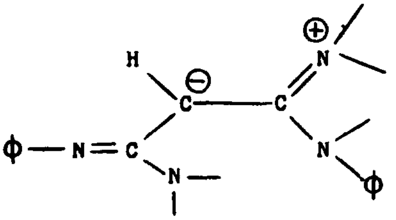
g 6H	2.18/s	2.05/s

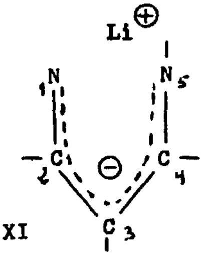
On the basis of inspection of models we assume, without actual proof, that the less hindered IXb is indeed the major component in the mixture.

By heating the sample of IX in the NMR tube to 70° coalescence between the absorptions of IXa and IXb was produced, as a result from free rotation around the C=C bond. Dipolar structures such as X probably reduce the strength of the C=C bond and therefore the free rotation could be reached at a relatively low temperature.

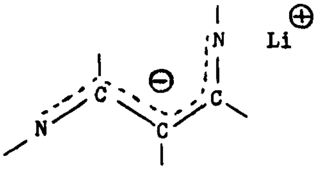


X

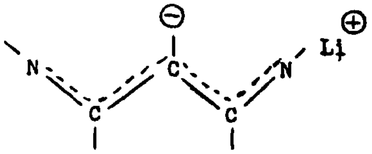
Thus, depending on the nature of the cation and the solvent, either exclusive C-methylation or exclusive N-methylation, of the anion derived from VI is obtained. One possible explanation to this phenomenon might be the existence of different conformations and different forms of coordination of the metal cation to the anion. Therefore, if Li$^{\oplus}$ in THF/ether solution is coordinated to the two nitrogen atoms that carry at least part of the negative charge, then it is assumed that the anion takes the U conformation XI. According to MO calculations[7] and experimental studies[8] on the pentadienylic system of 5 carbon atoms the U conformation would have been favored for the carbanion, unless interactions between substituents on carbons 1 and 5, or interactions with the solvent render the W and Sickle conformations more common. Such interactions are minimized in XI in which the nitrogens at positions 1 and 5 are linked only to one substituent. The $Li^{\oplus}$ is probably situated between these nitrogens and therefore the electrophilic attack to produce VII is on the carbon at position 3.



XI



XII



XIII

A different situation exists when the cation is $Na^{\oplus}$ and the solvent is ammonia. In this case it might be that the open conformations Sickle XII and W XIII are prefered, either because of the larger size of the cation or due to possible interactions between the solvent molecules and the nitrogen atoms of the anion. The result is an electrophilic attack on the electron rich nitrogens to produce the two isomers of IX.

The generality of these reactions might be of synthetical importance and is now under investigation for aliphatic malondiamidines.

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