Phosgene Immonium Salts. XIII. Dichloromalonyl Cyanines and 3,5-Bis(dimethylamino)pyrazoles

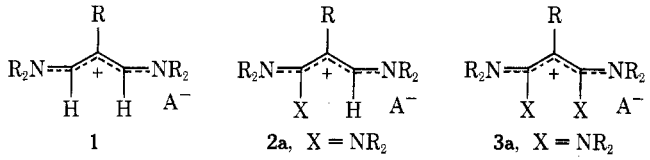
Guy J. de Voghel, Terry L. Eggerichs, Zdenek Janousek, and Heinz G. Viehe*

Laboratoire de Chimie Organique, Université de Louvain, B-1348 Louvain-la-Neuve, Belgium

Received March 2, 1973

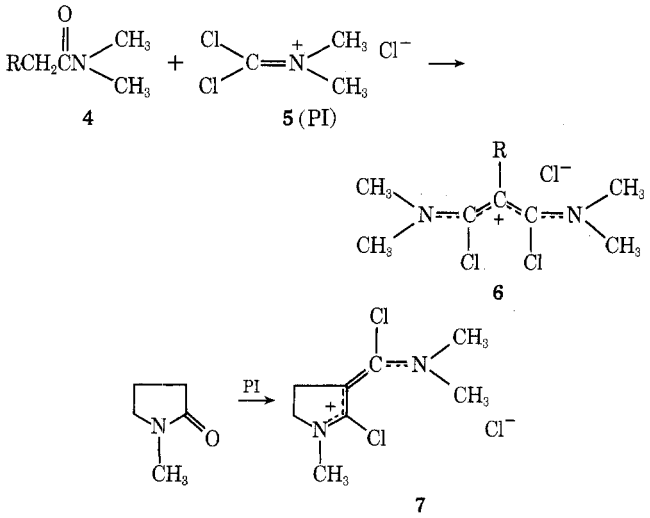
The chloromalonyl cyanine derivatives, **6**, were synthesized by the reaction of α-substituted *N,N*-dialkylacetamides with phosgene immonium chlorides. The biselectrophilic system in **6** is of general applicability to the synthesis of aminated heterocyclic systems. As the first example, the reactions of a variety of hydrazines with **6** are described. The corresponding 3,5-bis(dialkylamino)pyrazoles, **9**, are formed in good yield.

Cyanines (trimethinium salts) of the general structure **1** are well-known compounds, and have been widely used in synthesis. Vinylogous guanidinium salts **2a**[1] and the corresponding chloro derivatives **2b**[2] are also readily available, but previous efforts to obtain cyanines **3** at the oxidation level of malondiamide have been unsuccessful. Reactions of malondiamide with alkyl sulfates[3] or trialkyloxonium salts[4] give only monoactivated derivatives. Attempts to convert N,N′-tetrasubstituted malondiamides to bis(amide chlorides) (**3**, X = Cl) with a $TiCl_4$–dialkylamine complex furnished ill-defined products believed to be chelates;[5] with $POCl_3$, only one amide chloride function is introduced.[6] The use of phosphorus halides for these reactions would be expected to give the monoamide chloride, since reactions of this type are extremely sensitive to electron-attracting substituents. Although malondithioamides[7] and bis(dialkylamino)dithiolium compounds[8] have found some use in the synthesis of bis(dialkylamino)heterocycles, their general availability is limited.



1 **2a**, X = NR_2; **b**, X = Cl **3a**, X = NR_2; **b**, X = OR

As a source of synthon **3** we have developed a general and convenient preparation of the dichloromalonylcyanines **6**[9] by condensation of the powerfully electrophilic phosgene immonium (PI) salts **5** with N,N-disubstituted amides. Amides without α hydrogen are readily converted to amide chlorides by the PI reagent.[10] With monosubstituted acetamides, further condensation to the malonyl cyanines **6** occurs even at low temperatures and with deficient amounts of the PI salt. *N*-Methylpyrrolidine gives the cyclic analog **7**.

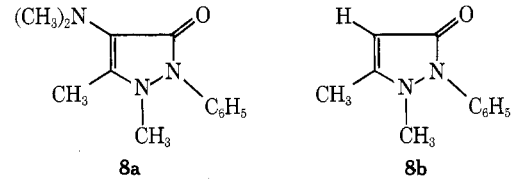


4 **5** (PI) **6** **7**

The method is quite general and leads to cyanines **6** with R = alkyl, aryl, halo, and alkoxy substituents; the reaction fails with bulky groups such as *tert*-butyl and R_3N^+-. The cyanines that have been prepared are listed in Table I. For characterization the cyanines were hydrolyzed with aqueous bicarbonate to the N,N-tetrasubstituted malondiamides.

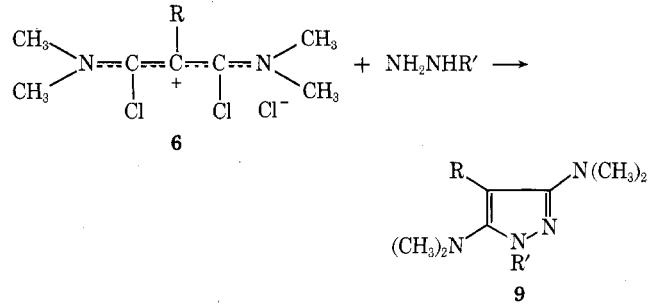
The dichloromalonylcyanines are stable yellow solids, soluble in chloroform but insoluble in ether. The extended charge delocalization in these compounds is reflected in their spectral properties. For the unsubstituted cyanine (**6**, R = H), the uv absorption maximum is at 346 nm; alkyl substitution causes a bathochromic shift of 42 nm, and groups that can exert a positive mesomeric effect (OR, Cl, C_6H_5, etc.) cause a further shift of 20–30 nm. As expected for the completely delocalized cyanine structure, the four NCH_3 groups give rise to a single CH_3 resonance at δ 3.4–3.7 ppm in the nmr spectra of **6**. The ir spectra of **6** shows no absorption from 1600 to 1800 cm^{-1}; a characteristic band appears at 1550 cm^{-1}.

The synthetic utility of the malonyl cyanines is borne out by their conversion to a variety of malonic acid derivatives and 1,3-bis(dialkylamino) heterocycles.[10] A particularly effective application is the reaction with hydrazines to give a variety of 4-substituted-3,5-bis(dialkylamino)pyrazoles. A limited number of 3,5-bis(amino)pyrazoles have been obtained by various condensation routes,[7,8,11] but these routes are of limited scope. The enhanced activity of aminopyrine **8a** compared to antipyrine **8b** exemplifies the potential value of the dialkylamino pharmacophore.[12]



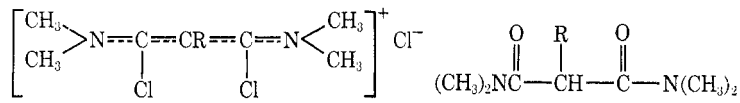
8a **8b**

The malonyl cyanines **6** were condensed directly with a variety of hydrazines in refluxing chloroform or dichloromethane. Bis(dimethylamino)pyrazoles **9** were obtained in



6 **9**

Table I
Dichloromalonyl Cyanines 6 and Malondiamides 10[a]

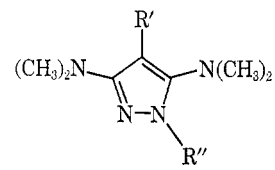


6 10

R	Registry no.	Yield, %	Uv max (CH_2Cl_2)	Malondiamide mp, °C	Registry no.
H	34057-61-9	91	346		
CH_3	50859-92-2	90		69–70	50859-98-8
C_2H_5	34057-62-0	88	388	75–76	33564-08-8
C_6H_5	34057-63-1	90	397	149[b]	33564-09-9
Cl	34112-12-4	88	410	92	33564-10-2
OCH_3	50859-93-3	95	406	63	50859-99-9
OC_2H_5	50859-94-4	98	409	76	50860-00-9
$OCH(CH_3)_2$	50859-95-5	92	407	53	50860-01-0
OC_6H_5	50859-96-6	99	406	116	50860-02-1
$OCOCH_3$	50859-97-7	60	392	82 (0.04 mm)[c]	50860-03-2

[a] Satisfactory analytical data (±0.4% for C, H) were obtained for malonyldiamides. [b] Lit. mp 150°: R. Burguda, *C. R. Acad. Sci.*, **258**, 1532 (1964). [c] Boiling point.

Table II
3,5-Bis(dimethylamino)pyrazoles 9



Registry no.	Compd	R′	R″	Yield, %	λ_{max} (EtOH[e]), nm (ε)	Mp or bp, °C (mm)
50860-04-3	**9a**	H	CH_3	82[c]	244 (8800)[f]	118 (0.4)
50860-05-4	**b**	H	C_6H_5	92[c]	290 (7000)	120 (0.3)
50860-06-5	**c**[a]	H	C_6H_5	90[c]	292 (8800)	125 (0.3)
50860-07-6	**d**	H	$CO_2C_2H_5$	72[c]	260 (13,700)	84 (petroleum ether) 126 (0.4)
50860-08-7	**e**	H	2,4-$(NO_2)_2C_6H_3$	89[c]		159–160 (MeOH)
50860-09-8	**f**	C_6H_5	$CO_2C_2H_5$	72[c]	280 (12,000)	130 (0.4)
50860-10-1	**g**	Cl	C_6H_5	85[c]	280 (9600)	130 (0.4)
50860-11-2	**h**	OCH_3	$CO_2C_2H_5$	92[d]	273 (10,300)	115–120 (0.4)
50860-12-3	**i**	OCH_3	$SO_2C_6H_5$	90[d]	270 (6500)[g]	76 (EtOH)
50860-13-4	**j**	OCH_3	C_6H_5	82[d]	284 (11,400)	68 (CCl_4)
50860-14-5	**k**	OC_2H_5	$CO_2C_2H_5$	95[d]	275 (13,800)	115–120 (0.4)
50860-15-6	**l**	OC_2H_5	$SO_2C_6H_5$	95[d]	274 (7800)	86 (Ether)
50860-16-7	**m**	OC_2H_5	C_6H_5	86[d]	288 (10,500)[g]	51 (Petroleum ether)
50860-17-8	**n**	O-*i*-C_3H_7	C_6H_5	78[d]	289 (11,500)[g]	89 (Ether)
50860-18-9	**o**	OC_6H_5	$CO_2C_2H_5$	98[d]	275 (7600)	72 (Ether)
50860-19-0	**p**	OC_6H_5	$SO_2C_2H_5$	73[d]	274 (9600)[g]	112 (MeOH)
50860-20-3	**q**	OC_6H_5	C_6H_5	93[d]	277 (15,500)[h]	90 (MeOH)
50860-21-4	**r**	OC_6H_5	H	32[b,d]	240 (8270)	160 (Ether)
50860-22-5	**s**	OC_6H_5	CH_3	78[d]	243 (7200)	125 (0.4)

[a] Bis(diethylamino) analog of **9**. [b] Obtained as a by-product (maximum yield) in the reaction to form **9**. [c] Condensation was carried out in $HCCl_3$. [d] Condensation was carried out in CH_2Cl_2. [e] Or as otherwise indicated. [f] $CHCl_3$. [g] CH_2Cl_2. [h] CH_3OH.

70–90% yield (Table II). The use of bases such as tertiary amines was not required, and their use resulted in lower yields. The pyrazoles were liberated from the hydrochlorides by aqueous base. In one condensation of benzenesulfonyl chloride, cleavage to give the unsubstituted pyrazole and the sulfonyl chloride was observed. With 1,1-dimethylhydrazine, dealkylation occurred to give the 1-methylpyrazole.

Experimental Section

Melting points were taken in open capillary tubes and were uncorrected. Boiling points recorded for molecular distillations were of the oven temperatures. The uv spectra were recorded on a Unicam SP1800 spectrometer, ir spectra were obtained using a Perkin-Elmer 237, and nmr spectra were recorded on a Varian T60 spectrometer at room temperature with TMS as internal standard.

Malonyl Cyanines and Their Hydrolysis Products. The same general procedure was used for all the malonyl cyanines. Phosgene immonium chloride (0.2 mol) and the amide (0.1 mol) were combined in chloroform or dichloromethane (100 ml), and the mixture was refluxed until all the phosgene immonium chloride had dissolved and HCl evolution had ceased. The reaction was protected by a drying tube ($CaCl_2$) at all times. The solvent was removed under vacuum, and the residue was washed with several portions of dry ether until all of the dimethylcarbamoyl chloride was removed. The cyanines, which in most instances crystallized upon stirring with ether, were characterized by hydrolysis to the corresponding malondiamide. The cyanines were soluble in chloroform or dichloromethane, but were insoluble in ether. The nmr spectra contained a single NCH_3 peak at 3.6–3.7 ppm.

The malonyl cyanines (0.05 mol) were dissolved in water (20 ml), and solid potassium carbonate was added until the yellow color of the cyanine disappeared and the solution remained basic. The mixture was extracted with ether, the organic extract was dried ($CaCl_2$), and the ether was evaporated. The resulting residues were crystallized from ether–petroleum ether (bp 40–60°).

1-Dimethylamino-1,3-dichloro-3-methylamino(*N*-2-ethylene)-trimethinium Chloride (7). *N*-Methylpyrrolidone (2.5 g, 25 mmol) and phosgene immonium chloride (8.1 g, 50 mmol) were refluxed in 50 ml of dry chloroform until all solid had dissolved. The solvent was then removed to give 6.01 g (98%) of 7 as a dense oil: nmr ($CDCl_3$) δ 4.39 (2 H, t, J = 10 Hz), 3.43 (9 H, s), 3.40 (2 H, t); uv (CH_2Cl_2) λ_{max} 381 nm (ϵ 5500).

3-(*N,N*-Dimethylcarbamoyl)-*N*-methyl-2-pyrrolidone. The cyanine 7 (6.00 g, 24.7 mmol) was dissolved in 20 ml of chloroform and stirred with 5 ml of water and an excess of $NaHCO_3$ for 1 hr. The organic phase was collected, dried over $MgSO_4$, and evaporated. Distillation gave 3.6 g (87%) of 7: bp 114° (0.5 mm); nmr ($CDCH_3$) δ 3.27 (3 H, s), 3.00 and 2.88 (6 H, 2 s), and a complex second-order pattern between 2.0 and 4.0 ppm (4 H); mass spectrum m/e 170 (M^+), 142, 126, 98.

General Procedure for Pyrazole Formation. The cyanine 6 (0.01 mol) and the hydrazine (0.011 mol) were combined in chloroform or dichloromethane (75 ml) and the reaction mixture was refluxed until the yellow color of the cyanine disappeared. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. Aqueous potassium hydroxide (2 *N*) was added to liberate the free pyrazole, and the resulting mixture was extracted with dichloromethane (5 × 100 ml). The organic phase was dried (Na_2SO_4), the solvent was evaporated, and the crude pyrazole was purified either by crystallization or by molecular distillation; characteristics of the pyrazoles are given in Table I. The nmr spectra of all 1-substituted 3,5-bis(dimethylamino)pyrazoles had two six-proton singlets at 2.6–2.7 and 2.8–2.9 ppm; 4-unsubstituted compounds had a one-proton singlet at 5.2–5.3 ppm; peaks due to substituents were present at the expected positions in all spectra; all pyrazoles gave satisfactory analytical data (±0.3% for C and H or ±0.003 Daltons by mass spectrum). The general procedure above gave only poor yields of **9s**. For this reason **9s** was made by two alternate procedures:

Procedure 1. Methyl hydrazine (0.01 mol) in dioxane (50 ml) was slowly added to the phenoxycyanine 6 (R = OC_6H_5) (0.01 mol) in CH_2Cl_2 (25 ml) with stirring at −8°. The reaction mixture was stirred overnight, the precipitated salts were filtered off, and the organic solvent was evaporated under suction. The residue was dissolved in a minimal amount of water, and 2 *N* KOH was added to liberate the free pyrazole. The aqueous mixture was extracted with ether (5 × 100 ml), the ethereal solution was dried (Na_2SO_4), and the solvent was evaporated. The resulting residue was distilled horizontally to give 2.04 g (78%) of **9s**.

Procedure 2. The phenoxycyanine (0.01 mol) in $CHCl_3$ (50 ml) and *N,N*-dimethylhydrazine (0.02 mol) in $CHCl_3$ (25 ml) were combined slowly with stirring at 0°. After 1 hr the solution was refluxed until the yellow color of the cyanine disappeared. The dimethylhydrazine hydrochloride was filtered off and the solvent was evaporated under suction. The residue was dissolved in a minimal amount of water and 2 *N* KOH was added to liberate the free pyrazole. Further work-up was carried out as in procedure 1 to give 1.25 g (48%) of **9s**.

Acknowledgment. The authors express their thanks to the Badische-Anilin & Soda Fabrik for material support, Professors Emile Dubois and Paul Cadiot of the University of Paris for fellowship, and the Institut pour l'Encouragement de la Recherche Scientifique dans l'Industrie et l'Agriculture for a "bourse de specialisation" granted to G. J. de Voghel. Particular thanks are due to Dr. F. Compernolle for his high-resolution mass spectroscopy.

Registry No.—4 (R = H), 127-19-5; 4 (R = CH_3), 758-96-3; 4 (R = C_2H_5), 760-79-2; 4 (R = C_6H_5), 18925-69-4; 4 (R = Cl), 2675-89-0; 4 (R = OCH_3), 4128-76-1; 4 (R = OC_2H_5), 24475-96-5; 4 [R = $OCH(CH_3)_2$], 50860-23-6; 4 (R = OC_6H_5), 10397-59-8; 4 (R = $OCOCH_3$), 13831-28-2; **5**, 33842-02-3; **7**, 50860-24-7; NH_2NHR' (R′ = CH_3), 60-34-4; NH_2NHR' (R′ = C_6H_5), 100-63-0; NH_2NHR' (R′ = $CO_2C_2H_5$), 4114-31-2; NH_2NHR' [R′ = 2,4-$(NO_2)_2C_6H_3$], 119-26-6; NH_2NHR' (R′ = $SO_2C_6H_5$), 80-17-1; NH_2NHR' (R′ = $SO_2C_2H_5$), 37984-88-6; NH_2NHR' (R′ = H), 302-01-2; *N*-methylpyrrolidone, 872-50-4; 3-(*N,N*-dimethylcarbamoyl)-*N*-methyl-2-pyrrolidone, 50932-75-7.

References and Notes

(1) C. Jutz and E. Müller, *Angew. Chem., Int. Ed. Engl.*, **5**, 724 (1966).
(2) Z. Arnold, *Collect. Czech. Chem. Commun.*, **72**, 956 (1960); H. G. Viehe, T. Van Vyve, and Z. Janousek, *Angew. Chem., Int. Ed. Engl.*, **11**, 916 (1972).
(3) H. Bredereck, F. Effenberger, and H. P. Beyerlin, *Chem. Ber.*, **97**, 3076 (1964).
(4) H. Hafner, K. Bangert, and V. Orfanos, *Angew. Chem., Int. Ed. Engl.*, **6**, 451 (1967).
(5) H. Weingarten and W. White, *J. Org. Chem.*, **31**, 2874 (1966).
(6) H. Bredereck and K. Bredereck, *Chem. Ber.*, **94**, 2278 (1961).
(7) G. Barnikow, *Justus Liebigs Ann. Chem.*, **700**, 46 (1966).
(8) G. Barnikow, *Chem. Ber.*, **100**, 1389 (1967).
(9) Preliminary communication: Z. Janousek and H. G. Viehe, *Angew. Chem., Int. Ed. Engl.*, **10**, 574 (1971).
(10) For a summary of reactions of PI reagents, see H. G. Viehe and Z. Janousek, *Angew. Chem.*, **85**, 837 (1973); *Angew. Chem., Int. Ed. Engl.*, **12**, 806 (1973).
(11) P. Schmidt and J. Drury, *Helv. Chim. Acta*, **39**, 986 (1956).
(12) W. E. Coyne in "Medical Chemistry," 3rd ed, A. Burger, Ed., Wiley-Interscience, New York, N. Y., 1970, p 960.

Hydrogen Cyanide Chemistry. VII. Diiminosuccinonitrile Condensation with Diaminomaleonitrile[1]

R. W. Begland, D. R. Hartter, D. S. Donald,* A. Cairncross, and W. A. Sheppard

Contribution No. 2015 from the Central Research Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

Received January 15, 1974

Diiminosuccinonitrile (DISN) condenses with diaminomaleonitrile (DAMN) to give tetracyanopyrazine, aminotricyanopyrazine, and 2,3-diamino-5,6-dicyanopyrazine. By choice of conditions any one of these tetrafunctional pyrazines can be the major product; linear 1:1 and 2:1 adducts are formed under other conditions and the 1:1 adduct can be cyclized to the pyrazines. DISN reacts with 1 mol of water to form an intermediate, probably iminooxalyl cyanide, which condenses with DAMN to give 2-amino-3-hydroxy-5,6-dicyanopyrazine. Two moles of water hydrolyze DISN to oxalyl cyanide, which condenses with DAMN to give tetracyanopyrazine under acidic conditions and 1,4,5,6-tetrahydro-5,6-dioxo-2,3-dicyanopyrazine under neutral conditions.

Diiminosuccinonitrile (DISN) and diaminomaleonitrile (DAMN) are now readily available research chemicals derived from hydrogen cyanide.[2] We have previously shown that nucleophiles displace either ammonia or hydrogen cyanide from DISN under varying conditions.[3] This behavior is further exemplified by the reactions of DISN with DAMN by which various tetrasubstituted pyrazines