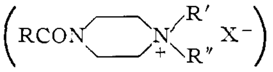
TABLE I

DERIVATIVES OF MONOACYLPIPERAZINES 

Compound	R	R'	R"	X	M.p., °C.	Empirical Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I	Ph_2CH	Me	H	Cl	265 d.[b,h]	$C_{19}H_{23}ClN_2O$	69.0	68.4	7.0	6.8
II	Ph_2CH	Me	Me	I	223.5[b,h]	$C_{20}H_{25}IN_2O$	55.1	54.6	5.7	5.6
III	Ph_2CH	Me	Et	I	228[b,h]	$C_{21}H_{27}IN_2O$	56.0	56.1	6.0	6.3
IV	Ph_2CHCH_2	$PhCH_2$	H	Cl	255[c]	$C_{26}H_{29}ClN_2O$	74.2	73.7	7.0	6.7
V	Ph_2CHCH_2	H	H	Cl	224[c]	$C_{19}H_{23}ClN_2O$	69.0	68.7	7.0	7.2
VI	Ph_2CHCH_2	Me	H	Cl	264 d.[c,f]	$C_{20}H_{25}ClN_2O$	69.6	69.8	7.3	7.2
VII	Ph_2CHCH_2	Me	Me	I	260[c]	$C_{21}H_{27}IN_2O$	56.0	55.4	6.0	6.0
VIII	Ph_2CHCH_2	Me	Et	I	218[c]	$C_{22}H_{29}IN_2O$	56.9	57.0	6.3	6.3
IX	Ph_2CHCH_2	Me	*i*-Pr	I	198[b]	$C_{23}H_{31}IN_2O$	57.7	57.5	6.5	6.5
X	Ph_2CHCH_2	Me	*n*-C_4H_9	I	223[c]	$C_{24}H_{33}IN_2O$	58.5	58.3	6.8	6.8
XI	Ph_2CHCH_2	Et	Et	I	235[c]	$C_{23}H_{31}IN_2O$	57.7	57.1	6.5	6.5
XII	$(CH_2)_5CPh$-	Me	H	Cl	268[b,g]	$C_{18}H_{27}ClN_2O$	66.9	67.0	8.4	8.4
XIII	$(CH_2)_5CPh$-	Me	Me	I	248[d]	$C_{19}H_{29}IN_2O$	53.3	53.0	6.8	7.0
XIV	$(CH_2)_5CPh$-	Me	Et	I	206[d]	$C_{20}H_{31}IN_2O$	54.3	54.1	7.1	7.0
XV	$(CH_2)_5CPh$-	Me	*i*-Pr	I	172[b]	$C_{21}H_{33}IN_2O$	55.2	55.0	7.3	7.5
XVI	$C_{13}H_9O$[a]	Me	Et	I	244 d.[e]	$C_{21}H_{25}IN_2O_2$	54.3	54.2	5.4	5.6
XVII	$C_{13}H_9O$[a]	Et	Et	I	246 d.[e]	$C_{22}H_{27}IN_2O_2$	55.2	55.3	5.7	5.8
XVIII	$C_{13}H_9O$[a]	Me	*i*-Pr	I	256 d.[e]	$C_{22}H_{27}IN_2O_2$	55.2	55.7	5.7	5.8

[a] 9-Xanthenyl. [b] Crystallized from abs. ethanol. [c] Crystallized from aqueous ethanol. [d] Crystallized from ethanol–ether mixtures. [e] Crystallized from methanol. [f] The base crystallizes from benzene–hexane and melts at 98°. [g] The base melts at 96–98°. [h] Reported after the conclusion of this work by O. Hromatka, O. Kraupp and L. Stentzel, *Monatsh.*, **85**, 1208 (1954).

N-(β,β-Diphenylpropionyl)-piperazine (V).—The above hydrochloride was dissolved in 50 cc. of aqueous alcohol (95% ethanol + aq. hydrochloric acid) and hydrogenated over palladized charcoal. The reduction was slow and it was necessary to heat to about 60°. The hydrogen absorption was 22 mmoles (calcd. 20). The solution was removed from the catalyst, evaporated *in vacuo* and the solid residue was recrystallized from aqueous alcohol (yield 4.5 g.). This hydrochloride apparently retains moisture with great obstinacy and correct analytical figures could not be obtained directly. Those given in the table were obtained by correcting for moisture content: air-dried material was used in the combustion and a larger portion (100 mg.) of the same sample was dried at 0.02–0.04 mm. at 98°. The correction for moisture (4.3%) then was applied to the combustion figures.

N-(β,β-Diphenylpropionyl)-N'-diethylpiperazinium Iodide (XI).—Three grams of the secondary amine hydrochloride (V) was converted to the base. To this was added 3 cc. of ethyl iodide in 20 cc. of methanol, 6 g. of potassium carbonate and 5 cc. of water. The solution was refluxed 34 hours and the methanol was evaporated. The residue was washed with ether, filtered and the solid precipitate was washed with a little cold water. It was recrystallized from aqueous alcohol.

The N'-Methylpiperazine Amide of 1-Phenylcyclohexanecarboxylic Acid (XII).—In 20 cc. of dry benzene were dissolved 7.4 g. of 1-phenylcyclohexanecarboxylic acid chloride (0.033 mole) and 6.6 g. of methylpiperazine (0.066 mole). The reaction mixture was refluxed for 10 hours, cooled and partitioned between water and ether. The ethereal layer was then extracted with dilute hydrochloric acid from which 9.2 g. of water-insoluble base was precipitated by alkali. The hydrochloride was prepared by dissolving the base in absolute ethanol and adding a slight excess of ethanolic hydrogen chloride solution.

N-(1-Phenylcyclohexanecarbonyl)-N'-methyl-N'-ethylpiperazinium Iodide (XIV).—To 2.6 g. of the base XII in 20 cc. of acetone was added 25 cc. of 0.5 *M* ethyl iodide solution in ether. The solution was warmed gently on the steam-bath and the precipitated solid was recrystallized from ethanol–ether mixture. Correct analytical figures were obtained only after drying at 98° at 0.02 mm. pressure.

N-(Xanthene-9-carbonyl)-N'-methyl-N'-ethylpiperazinium Iodide (XVI).—One-tenth mole (21 g.) of xanthene-9-carboxylic acid was converted to the acid chloride by refluxing with excess thionyl chloride in benzene. When no more hydrogen chloride was evolved, the solvents were removed *in vacuo*, and the residual oil was dissolved in benzene. To it was added 20 g. of methylpiperazine and the resultant reaction mixture was refluxed one hour. After cooling, the material was partitioned between ether and water. The ethereal layer was then extracted with dilute hydrochloric acid from which the base was precipitated by addition of alkali. The solid base was washed with water and then dissolved in acetone. Excess ethyl iodide was added and the solution was warmed on the steam-bath for 9 hours. An oil had precipitated: the solvent was evaporated and ethanol was added whereupon the oil crystallized. The solid was recrystallized from methanol.

It will be observed that a number of the compounds reported in Table I furnished analytical figures that are not entirely satisfactory. Most of these deficiencies may be attributed to obstinate retention of moisture which is rather common with high-melting piperazine salts. In certain cases (compounds V and XIV above) these difficulties were surmounted. Compound XI may well have contained inorganic impurities.

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2-Phenylpyridines[1a,b]

BY GEORGE J. JANZ AND WILLIAM J. H. MCCULLOCH[2]

RECEIVED DECEMBER 1, 1954

The formation of mono-, di- and trimethylpyridines by the addition of acetonitrile to 1,3-dienes at 400° has been reported in a previous communication.[3] This note reports the results of some experiments extending the work to the synthesis of methyl substituted 2-phenylpyridines by the reaction of benzonitrile with butadiene, isoprene, 2-methylpentadiene and 2,3-dimethylbutadiene, respectively.

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(1) (a) Part IX in the series of papers entitled "The Reaction of Cyanogen and Related Nitriles with 1,3-Dienes"; (b) abstracted in part from the thesis submitted by W. J. G. McCulloch in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Chemistry), Rensselaer Polytechnic Institute, Troy, N. Y.

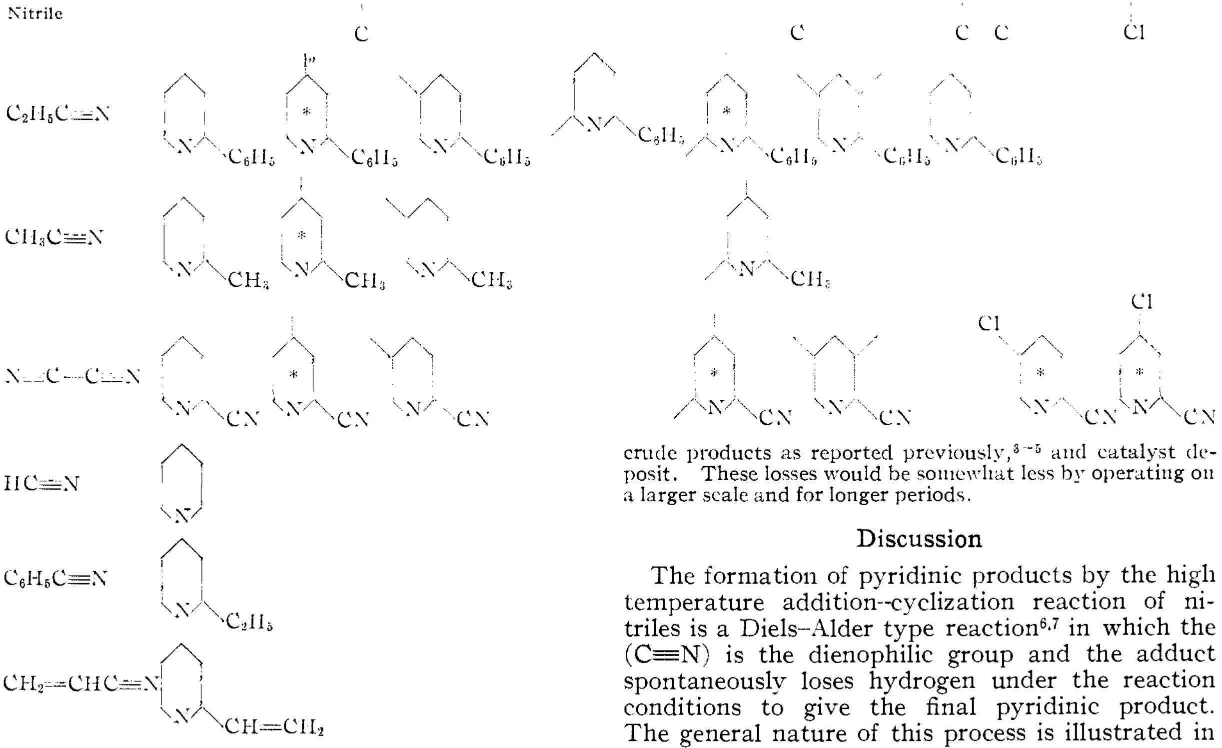
(2) Research Corporation Fellow in Chemistry, 1951–1953.

(3) G. J. Janz and S. C. Wait, Jr., THIS JOURNAL, **76**, 6377 (1954).

FIGURE I

PYRIDINES BY THE ADDITION OF NITRILES TO DIENES AT 400°

* The asterisk indicates the product found where two isomeric compounds were possible.



Experimental

A flow method was used for these experiments. In this method the reactants were fed continuously at a controlled rate through a catalyst bed at the reaction temperature. For investigation of novel reactions and yield data this method is applied more readily than the static processes. The apparatus and procedure were the same as used by Janz, McCulloch and Timpane for the catalyst search,[4] with one simplification. With liquid dienes, the reaction mixture was made to the desired molar ratio with benzonitrile by weight, and metered from only one flowmeter directly to the preheater and reactor assembly. The catalyst in each case was a very pure aluminum oxide (Harshaw Chem. Co., Al-0501) pretreated as described elsewhere.[5] The substituted dienes were samples commercially available, purified by distillation immediately before use. The benzonitrile and butadiene were of the same purity used before.[4]

The pyridinic products were separated for identification by aqueous extraction and steam distillation. The basic pyridinic oil thus separated in each case was purified by distillation under vacuum. The boiling point range and refractive index data are listed in Table I, together with the melting points (corrected) of the picrate derivatives. The composition of each product was confirmed by micro-analysis for nitrogen: 2-phenyl-4-methylpyridine, $C_{12}H_{11}N$ found 8.25, theor. 8.28; 2-phenyl-4,5-dimethylpyridine, $C_{13}H_{13}N$, found 7.57, theor. 7.65; 2-phenyl-4,6-dimethylpyridine, $C_{13}H_{13}N$, found 7.65, theor. 7.65.

A series of five experiments, each of two hours duration, was carried out to gain yield data in order to compare the relative reactivities of these dienes in this process. The operating data and yields are summarized in Table II. In each run the over-all material balance is 97–100%. No attempt was made to obtain data on the diene recovery since all yields were referred to the nitrile reactant. In addition to the pyridinic product, some of the nitrile was accounted for as ammonia (ammonium carbonate), present in the crude products as reported previously,[3-5] and catalyst deposit. These losses would be somewhat less by operating on a larger scale and for longer periods.

Discussion

The formation of pyridinic products by the high temperature addition–cyclization reaction of nitriles is a Diels–Alder type reaction[6,7] in which the (C≡N) is the dienophilic group and the adduct spontaneously loses hydrogen under the reaction conditions to give the final pyridinic product. The general nature of this process is illustrated in Figure I which summarizes the products found in the present investigation and earlier works. In the present study, as well as the products listed in Table I for isoprene and 2-methylpentadiene, the isomers, 2-phenyl-5-methyl- and 2-phenyl-3,5-dimethylpyridines, might be expected as possible products. In the case of the 2-methylpentadiene product, the sharp melting point of the picrate and agreement with the literature data confirmed the identity of this product; *i.e.*, very little, if any, of the 2-phenyl-3,5-dimethylpyridine had been formed in addition to the 2-phenyl-4,6-dimethylpyridine. The sharp melting point of the picrate for the product from the isoprene–benzonitrile reaction is also in accord with a product of one pure component rather than a mixture of isomers. Comparison with the products from the cyanogen, and acetonitrile reactions shows that this product is undoubtedly the 2-phenyl-4-methylpyridine. The melting point of the picrate reported elsewhere in the literature (Table I) is quite possibly in error. Further work is necessary to settle this point conclusively.

The space–time yields (Table II) on comparison show that isoprene, 2-methylpentadiene and 2,3-dimethylbutadiene are 1.5 to 2.0 times more reactive than butadiene. The pentadiene was a mixture of the *cis* and *trans* isomers, containing 70% of the latter. Accordingly, the reactivity of *trans*-pentadiene is more nearly that of 1,3-butadiene than the other dienes. These results, and the preferential formation of the 2-phenyl-4-methyl- and 2-phenyl-4,6-dimethylpyridines can be understood in

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(4) G. J. Janz, W. J. G. McCulloch and E. F. Timpane, *Ind. Eng. Chem.*, **45**, 1343 (1953).

(5) W. J. G. McCulloch and G. J. Janz, This Journal, **77**, 3014 (1955).

(6) P. J. Hawkins and G. J. Janz, *J. Chem. Soc.*, 1479 (1949).

(7) P. J. Hawkins and G. J. Janz, This Journal, **74**, 1790 (1952).

TABLE I

PHYSICAL PROPERTIES OF PHENYLPYRIDINES

Diene		Isoprene	1,3-Pentadiene	2,3-Dimethylbutadiene	2-Me-1,3-pentadiene
Pyridinic product		2-Ph-4-methyl-	2-Ph-6-methyl-	2-Ph-4,5-dimethyl-	2-Ph-4,6-dimethyl-
n^{25}D		1.6103	1.6059	1.6062 (35°)	1.5993
B.p., °C. (mm.)		110-115 (3)	117-120 (4)	146-150 (6)	130-134 (4)
Picrate, m.p., °C.	Obsd.	185-187	129-130	202-203	186-188
	Lit.	162[a]	135[c]	.....	186-187[b]

[a] L. Musajo and M. Colonna, *Gazz. chim. ital.*, **62**, 894 (1932). [b] R. L. Frank and R. P. Seven, THIS JOURNAL, **71**, 2629 (1949). [c] R. L. Frank and P. W. Meikle, *ibid.*, **72**, 4184 (1950).

TABLE II

REACTION CONDITIONS, MATERIAL BALANCE AND YIELDS

Activated Alumina, Al-0501, Catalyst

Reactants, Benzonitrile + Diene	T, °C.	Catalyst, cc.	Contact time, sec.	Mole ratio $\left(\frac{RCN}{Diene}\right)$	Material balance		Nitrile conversion (A), mole %	Pyridinic product		
					Total input, g.	Recov., g.		Total, g.	Yield, mole % calcd. on A	Space-time yield[a] $\times 10^4$
1,3-Butadiene	400	78	3.9	1.2	85.8	85.0	12	2.81	27	117
Isoprene	405	78	4.5	1.0	65.4	65.1	12	5.64	63	179
1,3-Pentadiene	397	92	4.2	1.0	109.6	108.5	28	1.71	9.0	55
2-Methyl-1,3-pentadiene	398	97.5	3.2	1.0	109.2	107.1	28	7.82	26	218
2,3-Dimethyl-1,3-butadiene	395	78	4.1	1.0	132.5	128.4	12	5.64	53	193

[a] Defined as moles/hr./100 cc. catalyst.

the light of the catalyzed reaction mechanism discussed in an earlier paper.[3]

The yields of phenylpyridines calculated on the nitrile conversions (Table II) undoubtedly can be improved with further study. Thus, using a chromia–alumina catalyst, 2-phenylpyridine has been obtained in 60 mole % yield[4] as compared to 27 mole % in this work. This reaction offers a ready method for the synthesis of these phenylpyridines in small amounts. In addition to simplicity, the method is specific for the desired product, a direct contrast to the more recognized procedures in which mixtures of pyridines are formed.

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The Preparation and Properties of 2-Chloro-2'-fluorodiethyl Sulfide[1]

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As part of a program to discover new methods for the preparation of organic fluorine compounds, 2-chloro-2'-fluorodiethyl sulfide has been prepared and its properties investigated.

Attempts have been made by some British investigators to prepare the fluorine analogs of "mustard gas" by the action of thionyl fluoride and anhydrous hydrogen fluoride on thiodiglycol. The experiments were conducted in metal containers, with and without solvents, at high and low temperatures. No volatile fluorine compounds were obtained.

We have succeeded in preparing fair yields of the monofluoro compound by the series of reactions

$$HOCH_2CH_2SCH_2CH_2OH + 2COCl_2 \longrightarrow \underset{\text{I}}{ClCOOCH_2CH_2SCH_2CH_2OCOCl} + 2HCl$$

$$\text{I} + HF \longrightarrow \underset{\text{II}}{ClCOOCH_2CH_2SCH_2CH_2OCOF} + HCl$$

$$\text{II} + \xrightarrow{\text{heat}} \underset{\text{III}}{ClCH_2CH_2SCH_2CH_2F} + 2CO_2$$

The formation of thiodiglycol bis-chloroformate (I) proceeds smoothly at 0°. The replacement of chlorine by fluorine and the subsequent elimination of carbon dioxide have not been studied sufficiently to determine the optimum conditions. The main product of the over-all reaction (as now carried out) is the partially fluorinated derivative (III). Small amounts of what appears to be difluorodiethyl sulfide are obtained in admixture with the monofluorinated derivative; it appears as a low-boiling fraction in the distillation of the reaction product. The reason for the preferential formation of the monofluoroformate II, even when hydrogen fluoride is present in excess, is unknown.

2-Chloro-2'-fluorodiethyl sulfide, b.p. 91.5–92.5° (30 mm.), f.p. −44°, is a colorless liquid with a very faint, mercaptan-like odor which is not unpleasant. The molecular refraction calculated from the density and refractive index agrees with the value calculated from the atomic refractivities.

Experimental Part

Thiodiglycol Bis-chloroformate.—Liquid phosgene (110 g., 1.1 moles) was placed in a 500-ml. round-bottom flask fitted with a dropping funnel and surmounted by a reflux condenser cooled with an acetone–Dry Ice mixture. While the flask was cooled in ice-water, thiodiglycol (55 g., 0.5 mole) was added slowly through the dropping funnel. During this addition, which required about one hour, there was a copious evolution of hydrogen chloride. After the flask had stood at room temperature for four hours, it was connected to a water-pump; the pressure was reduced to remove any hydrogen chloride and excess phosgene. The colorless residual liquid thus obtained contains the correct amount of chlorine calculated for thiodiglycol bis-chloro-

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[1] This work was done in 1942 for the Office of Scientific Research and Development under Contract No. OEMsr-394 with the University of Chicago.