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1-Azetines

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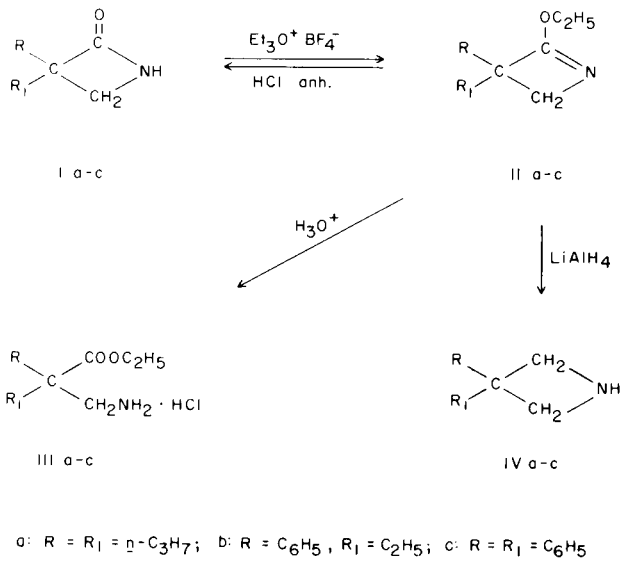
The synthesis, characteristics and chemical behaviour of some 3,3-disubstituted-2-ethoxy- and 2-ethylthio-1-azetines, the first examples of a new class of heterocyclic compounds, are described.

1-Azetines can be considered unknown, as no adequately characterized compounds containing a four-membered ring with a nitrogen atom and a double bond have been recorded (1). In fact, the assignment of the 1-azetine structure to the reaction product (2) between benzoyl bromide and silver cyanide is completely improbable. The general formula, 3-hydroxy-1-azetine-4-carboxylic acids, more recently assigned (3) to the condensation products between α-amino acids and glyoxal appears equally unlikely. Furthermore they were not adequately characterized from the chemical point of view. The novelty of 1-azetines and the possibility, suggested by Fowden and Bryant (4) that an 1-azetine derivative may be involved in the biosynthesis mechanism of azetidine-2-carboxylic acid (the only azetidine derivative isolated from natural sources) justifies the interest in the synthesis of this heterocyclic compound.

We have now found that 3,3-disubstituted azetidin-2-ones (I) (5) react readily with triethyloxonium fluoroborate (6) in methylene chloride at room temperature to give good yields of 3,3-disubstituted-2-ethoxy-1-azetines (II). Purification of compounds II has been carried out chromatographically on silica gel columns (method A), or by precipitation of the crystalline picrate and subsequent isolation of the base (II) using liquid ammonia (7) (method B).



a: R = R_1 = n-C_3H_7; b: R = C_6H_5, R_1 = C_2H_5; c: R = R_1 = C_6H_5

The 1-azetine structure II, in agreement with the elementary analysis data, has been confirmed by means of IR and NMR spectroscopy. The infrared spectra of compounds IIa-c show the absence of the β-lactam absorption at 1740-1750 cm^{-1} associated with I (5) and the presence of a band around 1620 cm^{-1}, attributed to the azetine C=N bond. As an example, the infrared spectrum of 3,3-diphenyl-2-ethoxy-1-azetine (IIc) in Nujol is reported (Fig. 1).

The NMR spectra of compounds IIa-c show (see Table I) the signals of the methylene of the ethyl group at 5.63-5.85 τ, in agreement with the -O-CH_2- structure. By comparison with known structures (Varian Catalog), the signal of a methylene bonded to an oxygen atom normally falls in the 5.22-6.50 τ range, while that bonded to a nitrogen atom is found in the 6.80-7.16 range. Moreover, a downfield chemical shift of the endonuclear -CH_2- group passing from compound IIa to IIc was observed and can be correlated with the change from an aliphatic to an aromatic type of the substituent at C_3. This behaviour falls within the general pattern of the effect of electronegative substituents on the chemical shift of protons (8).

The 2-ethoxy-1-azetines (II) are thermolabile substances, as was to be expected in view of the presence of a -CH=N- group in a highly strained ring. The stability is influenced by the type of substituents in position 3 and increases on passing from alkyl to aryl radicals. Compounds IIa and IIb are liquids and polymerize at room temperature, while 3,3-diphenyl-2-ethoxy-1-azetine (IIc) is solid and remains unaltered for long periods of time.

2-Ethoxy-1-azetines are colourless basic substances, soluble in petroleum ether. The picrates are stable and separate from petroleum ether solutions on treatment with picric acid. Their characteristics are reported in Table II together with the analytical data of the free bases IIa-c.

FIGURE 1

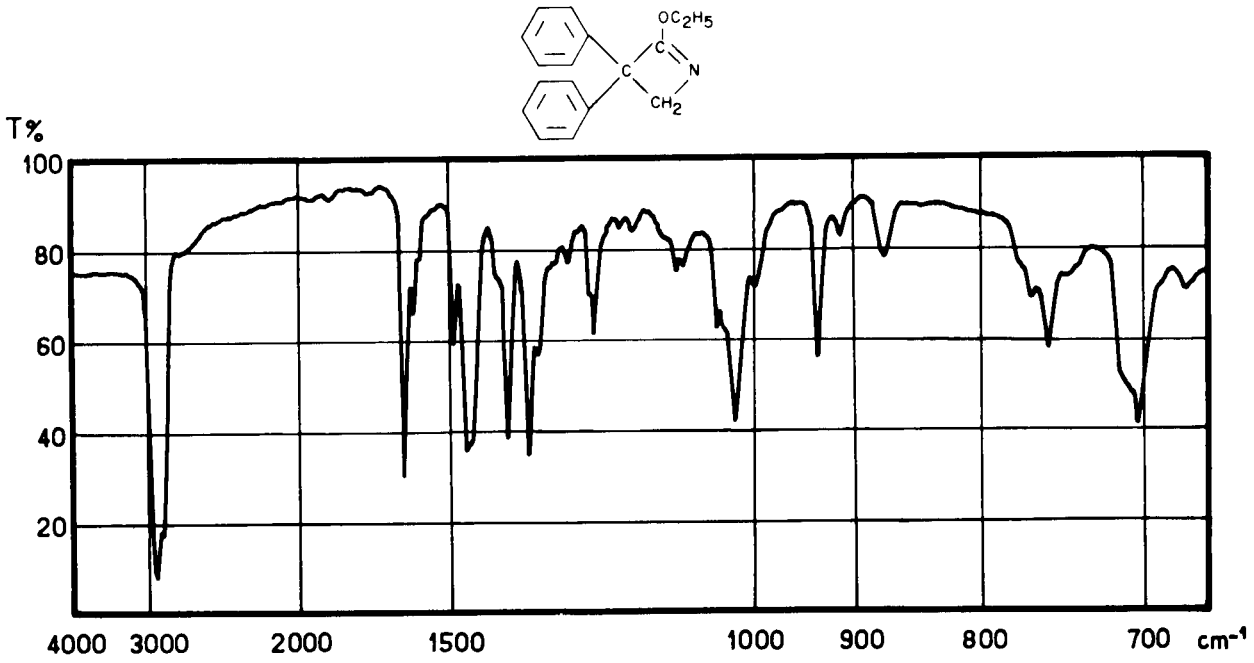


FIGURE 2

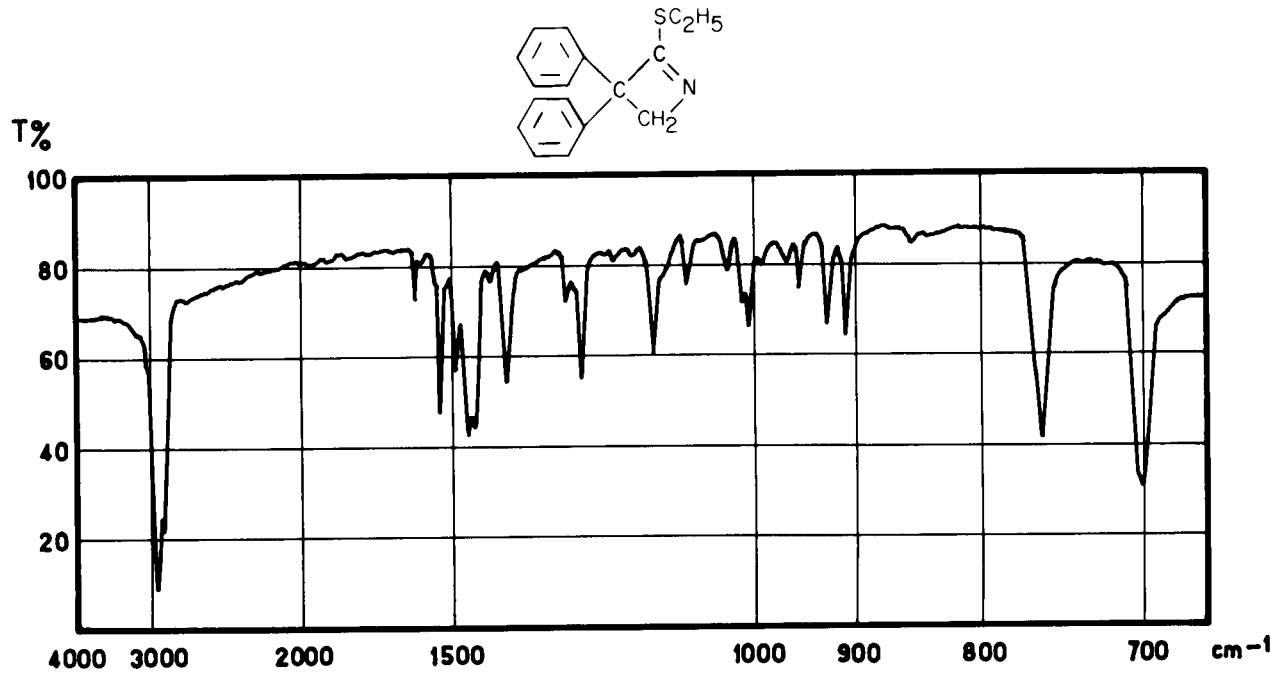
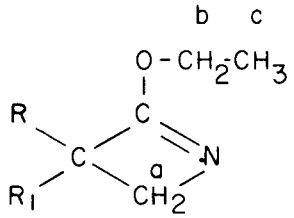
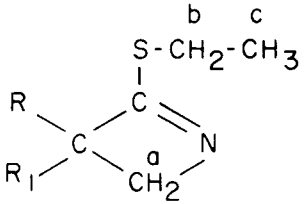


TABLE I

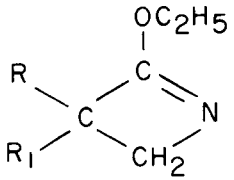
NMR Spectra (x) of II (a-c)  and VI (b-d) 

Compound	τ (p.p.m.)									
	CH_2				CH_3			CH	C_6H_5	C_6H_{11}
	a	b	d	f	c	e	g	h		
	d	d	e							
IIa $R = R_1 = CH_2\text{-}CH_2\text{-}CH_3$	7.10	5.85	8.85; 8.20	–	8.70	9.40-8.85	–	–	–	–
	f	g								
IIb $R = C_6H_5$; $R_1 = CH_2\text{-}CH_3$	6.64	5.68	–	8.11	8.63	–	9.13	–	2.76	–
IIc $R = R_1 = C_6H_5$	6.24	5.63	–	–	8.62	–	–	–	2.80	–
VId $R = H$; $R_1 = C_6H_{11}$	6.54; 6.29	7.06	–	–	8.69	–	–	~7.0		9.40-7.90
	f	g								
VIb $R = C_6H_5$; $R_1 = CH_2\text{-}CH_3$	6.15; 6.12	6.95	–	8.09	8.62	–	9.11	–	2.77	–
VIc $R = R_1 = C_6H_5$	5.75	6.90	–	–	8.60	–	–	–	2.79	–

(x) The NMR spectra were recorded with a Varian A-60 spectrometer (60 Mc/s.), in carbon tetrachloride solution with TMS as the internal reference (τ = 10.00 ppm).

TABLE II

3,3-Disubstituted 2-ethoxy-1-azetines (II)

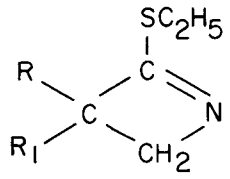


Compound II	R	R_1	Purif. proced. (a)	M.P. °C or B.P. °C/mm. Hg.	Formula	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	Nitrogen % Calcd.	Nitrogen % Found
IIa	n-C_3H_7	n-C_3H_7	B	50-52/0.15 (12)	$C_{11}H_{21}NO$	72.08	71.68	11.55	11.88	7.64	7.50
IIa-picrate			-	93-94	$C_{17}H_{24}N_4O_8$	49.51	49.30	5.87	6.00	13.58	13.28
IIb	C_6H_5	C_2H_5	A,B	80-81/0.1 (12)	$C_{13}H_{17}NO$	76.81	76.88	8.43	8.60	6.89	6.92
IIb-picrate (b)			-	138-140	$C_{19}H_{20}N_4O_8$	52.78	52.70	4.66	5.00	12.96	13.15
IIc	C_6H_5	C_6H_5	A,B	120/0.1 (12) (59-60)	$C_{17}H_{17}NO$	81.24	80.93	6.82	7.10	5.57	5.43
IIc-picrate (b)			-	138-139	$C_{23}H_{20}N_4O_8$	57.50	57.25	4.20	4.44	11.66	11.36

(a) A = chromatographic route; B = picrate route. (b) Picrates crystallized from ether-ethanol.

TABLE III

3-Substituted 2-ethylthio-1-azetines (VI)



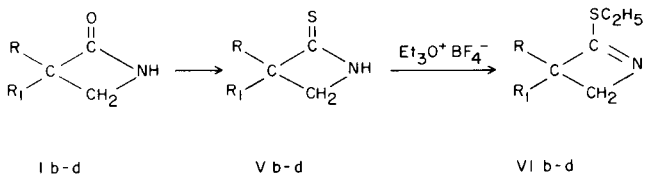
Compound	R	R_1	M.P. °C or B.P. °C/mm. Hg.	Formula	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	Nitrogen % Calcd.	Nitrogen % Found
VIb	C_6H_5	C_2H_5	105/0.15	$C_{13}H_{17}NS$	71.18	70.95	7.81	7.93	6.39	6.00
VIb-picrate (a)			167-168	$C_{19}H_{20}N_4O_7S$	50.88	50.79	4.50	4.66	12.49	12.35
VIc	C_6H_5	C_6H_5	70-72 (b)	$C_{17}H_{17}NS$	76.36	75.98	6.41	6.40	5.24	5.40
VIc-picrate (a)			195-197	$C_{23}H_{20}N_4O_7S$	55.64	55.46	4.06	4.16	11.29	11.19
VIc-hydrochloride			157 dec.	$C_{17}H_{17}NS{\cdot}HCl$	–	–	–	–	4.61	4.32
VId	C_6H_{11} (c)	H	90/0.10	$C_{11}H_{19}NS$	66.95	66.87	9.71	9.97	7.10	6.92
VId-picrate (a)			149-150	$C_{17}H_{22}N_4O_7S$	47.88	48.01	5.20	5.42	13.14	12.87

(a) Picrates crystallized from EtOH. (b) From hexane. (c) Cyclohexyl.

3,3-Disubstituted-2-ethoxy-1-azetines were soluble in dilute mineral acids, and behave essentially as cyclic imino-ethers. In fact, acid hydrolysis of the C=N bond with dilute hydrochloric acid led to cleavage of the ring, thus giving the corresponding ethyl α,α-disubstituted β-amino-propionate hydrochlorides (IIIa-c). 3,3-Diphenylazetidin-2-one (Ic) separated in very low yield, as a secondary product of the hydrolysis of IIc. This demonstrates that in this case the hydrolytic cleavage has occurred at the ether group in position 2. Treatment with anhydrous hydrochloric acid in ethereal solution caused only splitting of the *O*-ethyl group with regeneration of 3,3-disubstituted azetidin-2-ones (I).

Reduction of IIa-c with lithium aluminum hydride led to the formation of the corresponding 3,3-disubstituted azetidines (IV) (9). All of these experimental results agree with and confirm the assigned structures.

Sulfuration of *N*-unsubstituted azetidin-2-ones (I) into the corresponding azetidine-2-thiones (V) has recently been perfected in our laboratories (10). Compounds V react with triethyloxonium fluoroborate and gave excellent yields of the 3-substituted-2-ethylthio-1-azetines (VIb-d).



I b-d V b-d VI b-d

b: R = C_6H_5 ; R_1 = C_2H_5; c: R = R_1 = C_6H_5 ; d: R = cyclohexyl, R_1 = H

In accord with the analytical data, the 1-azetine structure of compounds VI has been demonstrated by IR spectroscopy. The infrared spectra of compounds VIb-d indicated the absence of the thio-β-lactam absorption associated with V (10) and the appearance of a band at approximately 1535 cm^{-1} was attributed to the azetine C=N bond. The infrared spectrum of 3,3-diphenyl-2-ethylthio-1-azetine (VIc) in Nujol (Figure 2) is reported as an example. The NMR spectra, in agreement with the assigned structure, are reported in Table I. Likewise in this case there was a displacement of the absorptions as a function of the substituents at C_3 analogous to what was observed for the corresponding 2-ethoxy-1-azetines (II).

Compounds VIb-d are more stable to heat and to chemical agents than the 2-ethoxy-1-azetines. For instance, unlike what occurs with compound IIc, 3,3-diphenyl-2-ethylthio-1-azetine (VIc) forms with aqueous hydrochloric acid a water-soluble hydrochloride from which compound VIc can be reobtained unaltered by the addition of alkali. Thus, compounds VI were easier to obtain: VIb and VId have been purified by distillation, while VIc has been crystallized. The analytical data for compounds VIb-d and of the corresponding picrates, are reported in Table III.

EXPERIMENTAL

General Procedure for the Preparation of 3,3-Disubstituted-2-ethoxy-1-azetines (IIa-c).

A solution containing 5.7 mmoles of 3,3-disubstituted azetidin-2-ones (Ia-c) in 10 to 15 ml. of methylene chloride was added dropwise at room temperature, with stirring, to a solution of 1.5 g. of triethyloxonium fluoroborate (11) in 5 ml. of methylene chloride. After the addition was completed (30 minutes), stirring was continued for an additional hour, then the solution was allowed to stand for two hours. The solution was washed with cold dilute sodium bicarbonate solution and finally with water, until neutral. It was dried over anhydrous sodium sulfate and the organic solvent was evaporated under reduced pressure without heating. The residue was dissolved in petroleum ether and any insoluble material removed by filtration. The solvent was distilled *in vacuo* and the product (IIa-c) purified according to one of the following techniques:

(A) Chromatographic Purification.

A column (internal diameter 18 mm) containing 25 g. of silica gel (0.05-0.2 mm) was used. The crude 1-azetine (1 g., IIb, IIc) was dissolved in 2 ml. of chloroform, then diluted with 8 ml. of petroleum ether and poured into the column previously washed with petroleum ether. The column was eluted with 250 ml. of chloroform/petroleum ether/methanol (5:90:5) mixture, in order to balance the column and to eliminate some impurities. The elution was then continued with a petroleum ether/methanol (90:10) mixture, collecting 25 ml. fractions. The first fraction was rejected and fractions 2, 3 and 4 containing the requisite pure product (IIb,IIc) were collected; yield 440 mg. for IIb; 520 mg. for IIc. 2-Ethoxy-1-azetine (II) was also present in the subsequent fractions (numbers 5 to 7), but was mixed with impurities.

(B) Purification via the Picrate.

An alcoholic solution of picric acid was slowly added to a clear solution of 2-ethoxy-1-azetine (IIa-c) in petroleum ether, until an acid reaction was obtained (checked with universal indicator paper). The mixture was cooled in an ice-water bath and the yellow precipitate was collected on a vacuum filter, washed on the filter itself with petroleum ether-ethyl alcohol. The picrate thus obtained, which may be further purified by recrystallization from ethanol-ether, was dried *in vacuo* at room temperature.

The analytical data of the picrates of the 3,3-disubstituted 2-ethoxy-1-azetines are recorded in Table II.

The base may be obtained from the picrate by dissolving the picrate in excess liquid ammonia and then allowing the liquid ammonia to evaporate at room temperature under anhydrous conditions (7). The residue was treated with anhydrous ether, the insoluble ammonium picrate was filtered off, and the filtrate concentrated to dryness (without heating). The residue was dissolved in petroleum ether, treated with charcoal, filtered and the solution concentrated *in vacuo*. Thus the pure base was obtained which can be quickly distilled *in vacuo* (12), operating with small quantities only. Distillation was always accompanied by marked decomposition.

The chemical and physical properties of the azetines thus obtained (IIa-c) are reported in Table II.

3,3-Diphenylazetidin-2-one (Ic) from IIc.

An ethereal solution of hydrochloric acid was added to a solution of 6 g. of 3,3-diphenyl-2-ethoxy-1-azetine in 50 ml. of anhydrous ether until acidic. An oil separated which redissolved immediately. The solvent was removed by distillation and the residue was precipitated with ether. The crude 3,3-diphenylazetidinone (4.5 g., m.p. 155-160°) was purified by recrystallization from ethanol (m.p. 169-171°). It was identical with an authentic sample (13).

Ethyl α,α-Diphenyl-β-aminopropionate (IIIc) from IIc.

A sample of 3,3-diphenyl-2-ethoxy-1-azetine (0.2 g.) was heated in 4 ml. of 10% hydrochloric acid on a boiling water bath for 90 minutes. The solution was cooled and the product was collected by suction filtration yielding 0.03 g. of 3,3-diphenylazetidin-2-one (Ic), melting point 169-171°, identical with an authentic sample (13).

The acid filtrate was concentrated under reduced pressure to dryness giving 0.15 g. of ethyl α,α-diphenyl-β-aminopropionate hydrochloride (IIIc), m.p. 192-194°. The water solution of the latter, made alkaline with potassium carbonate, yielded the free base which was identical with an authentic sample (13).

3,3-Diphenylazetidine (IVc) from IIc.

A solution of 900 mg. of 3,3-diphenyl-2-ethoxy-1-azetine in 10 ml. of ether was added dropwise, at room temperature, to a suspension of 400 mg. of lithium aluminum hydride in 15 ml. of anhydrous ether. The liquid was refluxed with stirring for 4 hours and then allowed to stand overnight at room temperature. It was cooled to -5° and the complex and the excess of reagent decomposed with the minimum quantity of 20% ammonium chloride solution. After filtering, the inorganic residue was washed with ether, and the filtrate was dried over sodium sulfate and concentrated under reduced pressure. The residue was distilled, collecting the fraction boiling at 125°/0.2 mm. Hg. It consisted of a colourless oil which rapidly crystallized. The infrared spectrum, the picrate (m.p. 220-223°, dec.) and the analytical data agree with those obtained from an authentic sample of 3,3-diphenylazetidine (14).

General Procedure for the Preparation of 3-Substituted-2-ethylthio-1-azetines (VIb-d).

A solution containing 7 mmoles of 3-substituted 2-thioazetidinones (Vb-d) (10) in 10 ml. of methylene chloride was added dropwise, at room temperature and with stirring, to a solution containing 1.8 g. of triethyloxonium fluoroborate (11) in 5 ml. of methylene chloride. Stirring was stopped and the solution, after standing overnight, was washed with cold 5% sodium hydroxide solution and then with water, until neutral, and finally dried over sodium sulfate. The solvent was distilled and the residue purified by distillation *in vacuo* (VIb-d) or by crystallization (VIc) from a suitable solvent (see Table III).

On addition of a saturated ethanolic picric acid solution, the corresponding picrates precipitated from an ethanol solution of the base and were purified by recrystallization from ethanol. The characteristics of these products, like those of the stable hydrochloride of VIc, obtained from the base by treatment with hydrochloric acid in ethereal solution, are recorded in Table III.

Acknowledgment.

The authors wish to express their appreciation to Dr. A. Vigevani, Dr. C. R. Pasqualucci and Dr. G. G. Gallo for infrared and nuclear magnetic resonance measurements and interpretation, to Mr. A. Restelli for the analytical work and to Dr. A. Wittgens for her assistance during the compilation of the manuscript.

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(11) Triethyloxonium fluoroborate, prepared according to H. Meerwein *et al.* (6), was stored under anhydrous ether in a refrigerator. At the moment of use, it was rapidly filtered (the substance is hygroscopic) through a sintered glass filter, weighed wet, and dissolved in the indicated solvent.

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Received June 5, 1967 Milano, Italia