

SEPARATION AND STUDY OF ISOMERIC ALDOXIMES OF THE PARAFFIN SERIES

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For the most part the study of the aldoximes from the point of view of stereoisomerism has been devoted to those in which the aldoximino group was attached to the benzene ring¹. Early investigators, in 1892, attempted to isolate the *syn* and *anti* aldoximes and to convert one form to the other², but since then little experimental work has been done to continue that research in the paraffin series. DUNSTAN AND DYMOND³ as well as BOURGEOIS AND DAMBMANN⁴ experienced great difficulty in the purification of acet-, propion-, valer- and iso-valeraldoximes, which suggested that two stereoisomeric forms were present, a liquid and a solid one, but attempts at their complete separation failed. On account of this the isomerism of aliphatic aldoximes has not been investigated further even by physical methods. Only PHYLLIPS⁵ in 1958, after inspecting the isomerism of four aldoximes with NMR, put forward the statement, anticipated long ago³, that aliphatic aldoximes are in an equilibrium state in solution, but believed, like others, that the single isolable pure form of aliphatic aldoximes is crystalline.

It therefore seemed of value that the isomerides of the aliphatic aldoximes should be isolated and studied so that physical methods could be applied to the elucidation of their stereochemical configuration.

We separated, by use of column and thin-layer chromatography, pure isomeric forms in the homologous series of aldoximes, from acet- to decanaloxime, including the branched isomers iso-butyr- and iso-valeraldoximes, and found that in the whole series the aldoximes exist in two forms: one *liquid* and one *crystalline*.

The isomers were eluted from the silica gel column with a mixture of petroleum ether-ethyl acetate. The course of separation was checked throughout on standard silica gel chromatoplates, in a developing solvent system of benzene-ethyl acetate with iodine vapour as visualising reagent. Liquid aldoximes (C₂-C₅) were subjected to the separation process immediately after distillation, and solid aldoximes (C₆-C₁₀) either from the crude mass after oximation or after standing at normal temperature for two days, since they showed one spot when freshly recrystallized, but in a day or two another spot could be detected pointing to the presence of two isomers.

Although the formation of co-ordination compounds has been suggested as a method for the determination of aromatic aldoxime configuration⁶, we could not find any regularity in the behaviour of aliphatic aldoximes towards metallic salts. Several conventional spray reagents were tried out, as can be seen from Table I.

The liquid isomers were first eluted from the silica gel column and their R_F values on chromatoplates were always higher than those of the solids (Table II, Figs. 1-5).

TABLE I
COLOUR REACTIONS OF ISOMERIC ALIPHATIC ALDOXIMES ON TLC
Solvent system: benzene-ethyl acetate (50:10, v/v)

Chromogenic reagents	iso											
	C ₂ *	C ₃	C ₄	C ₅	C ₆	C ₇	C ₈	C ₉	C ₁₀	C ₄	C ₅	
I ₂	l	c*	l	c	l	c	l	c	l	c	l	c
KMnO ₄ (0.5% aq.)	—	b**	b	b	b	b	b	b	b	b	b	b
H ₃ PO ₄ ·12 MoO ₃ ·x H ₂ O-ethanol	—	y	y	y	y	y	y	y	y	y	y	y
CuCl ₂ ·2H ₂ O (0.5% aq.)	—	g	g	g	g	g	g	g	g	g	g	g
Cu(CH ₃ COO) ₂ ·H ₂ O (0.5% aq.)	—	—	—	—	p	—	p	p	d	d	d	—
AgNO ₃ -ethanol	l	m	—	m	m	m	m	m	m	m	m	m

* l = liquid isomer; c = crystalline isomer.

** Designation of colours: b = brown; y = yellow; g = greenish blue when heated at 150°; p = pale green; d = dark green; l = light grey; m = mouse when heated at 110°.

TABLE II
 R_F VALUES AND PHYSICAL DATA OF ISOMERIC C_2-C_{10} ALDOXIMES

Compound	Physical constants		TLC R_F values $\times 100$		R_M values		Yield (%)	
	n_D^{22}	M.p. ($^{\circ}C$)	Liquid	Crystalline	Liquid	Crystalline	Liquid	Crystalline Mixture
Formaldoxime			45.0*		0.087			
Acetaldoxime	1.4258	47	16.4	9.3	0.706	0.990	9.8	15.8
Propionaldoxime	1.4292	39-40	48.6	42.8	0.024	0.125	17.0	21.2
Butyraldoxime	1.4342	36-38	50.7	44.3	-0.012	0.099	14.8	23.6
Valeraldoxime	1.4376	52	54.3	46.4	-0.075	0.062	17.1	26.0
Hexanaloxime	1.4411	49-50	57.1	47.8	-0.125	0.037	19.0	28.1
Heptanaloxime	1.4441	55	60.0	50.0	-0.176	0.000	21.5	26.2
Octanaloxime	1.4472	59-60	62.9	51.4	-0.228	-0.025	21.0	30.0
Nonanaloxime	1.4500	64	65.7	53.6	-0.283	-0.062	28.0	31.0
Decanaloxime	1.4534	68-69	68.6	55.7	-0.339	-0.099	30.0	38.0
Iso-butyraldoxime	1.4299	28-30	57.1	47.1	-0.125	0.050	25.2	15.4
Iso-valeraldoxime	1.4368	48	52.8	45.7	-0.050	0.075	16.4	25.8

* Formaldoxime can be detected with iodine only within 5 min after the oximation process, since it polymerizes afterwards.

The refractive indices of liquid isomerides showed a steady increase in the series from C_2 - C_{10} , with the exception of iso-butyraldoxime, which lies well off the straight line (Table II, Fig. 6). Great difficulty in separation was experienced with the liquid acetaldoxime isomer, on account of its great volatility and extreme tendency to interconversion. Therefore, its refractive index has to be taken with reserve.

All the liquid isomeric aldoximes are very unstable, being converted into the equilibrium mixture in 20-60 min. When kept at 0° , the stability is raised to 2 h and in very dilute solution at 0° up to 12 h.

The melting points of higher crystalline isomerides (C_5 - C_{10}) are found to be in accordance with those given in the literature⁷. Lower aldoximes are usually recorded as liquid, since the crystalline forms, sporadically obtained, were difficult to procure. This was the case with propionaldoxime and acetaldoxime³. However, for butyr- and iso-butyraldoxime only liquid forms were known. We revealed that the crystalline forms also existed melting at 36 - 38° and 28 - 30° , respectively (Table II).

The crystalline isomerides were somewhat more stable. The time of conversion ranged from 2 h (for C_2 - C_5) to two days (for C_8 - C_{10}) at 0° .

Although in the present investigation no attempt was made to find optimal conditions for separation of both isomerides, it could be deduced from the yields obtained that the distribution of isomers is in favour of solid isomer (Table II). One exception is encountered with iso-butyraldoxime and this is presumably due to a steric factor⁵.

By computing the R_M values⁸ of liquid as well as of solid isomers in normal series and plotting them against the number of carbon atoms in the oxime, an almost linear relationship is found (Fig. 7).

Thus, we could attribute further evidence for MARTIN'S⁹ additivity principle, since the mean values, although small, are in both oxime series as follows:

$$\Delta R_M(\text{CH}_2)\text{-liquid aldoxime} = 0.051 \pm 0.015$$

$$\Delta R_M(\text{CH}_2)\text{-crystalline aldoxime} = 0.031 \pm 0.007$$

"Anomalous" R_M values for the form- and acetaldoximes were discovered. According to MARCINKIEWICZ *et al.*¹⁰ this could be expected for just the first and second members of the series, where the constitutive interaction of the first CH_2 group with the functional group existed.

The comparison of R_M values with the number of carbon atoms in both series permitted the correlation of data obtained. We evaluated the mutual relation between two straight lines and obtained a conversion factor:

$$\Delta I = k_1 x + k_2$$

where ΔI is a "factor of geometrical isomerism", x the number of carbon atoms in the oxime, and k_1 and k_2 are calculated parameters, in these two series being 0.018 and 0.054, respectively. Such a factor is useful, since it typifies the mobilities of the respective pairs of isomers, and can be used in the form:

$$\Delta R_{M\text{-crystalline}} = R_{M\text{-liquid}} + \Delta I$$

for the calculation of an unknown isomer or for the "Isomerie Konstante" predicted by BRENNER AND PATAKI¹¹.

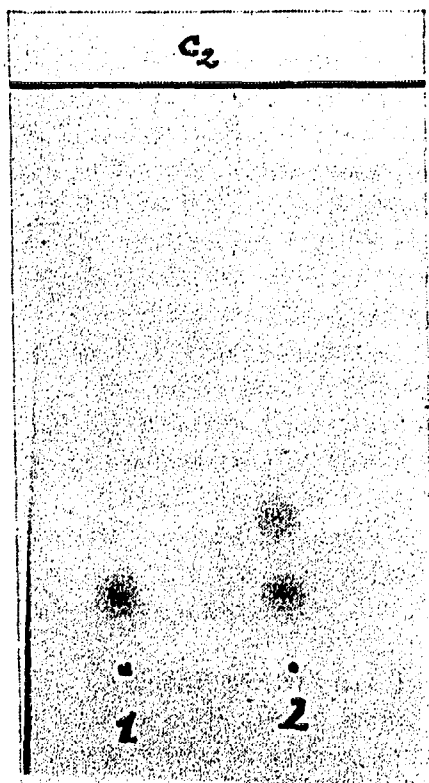


Fig. 1. TLC of acetaldoximes: liquid (1) and mixture of liquid and crystalline isomers (2).

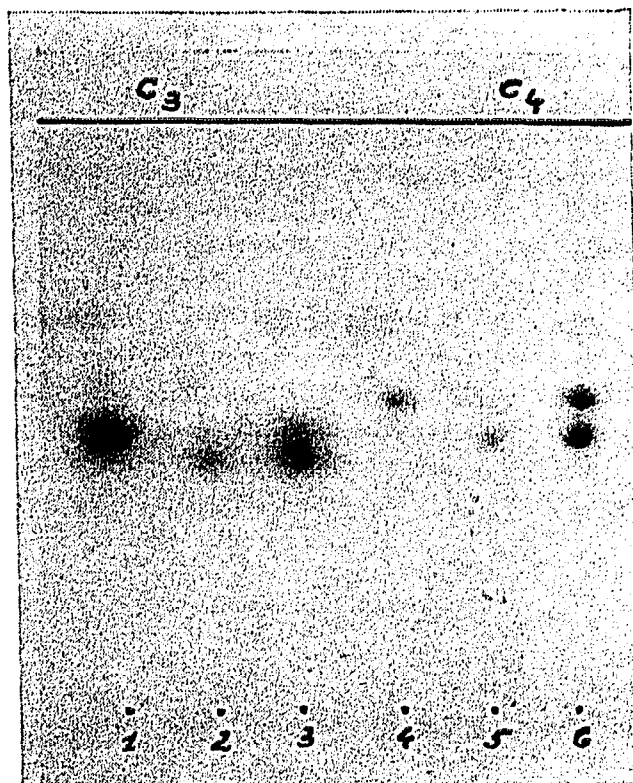


Fig. 2. TLC of liquid propionaldoxime (1), crystalline propionaldoxime (2), mixture of propionaldoximes (3), liquid butyraldoxime (4), crystalline butyraldoxime (5), mixture of butyraldoximes (6).

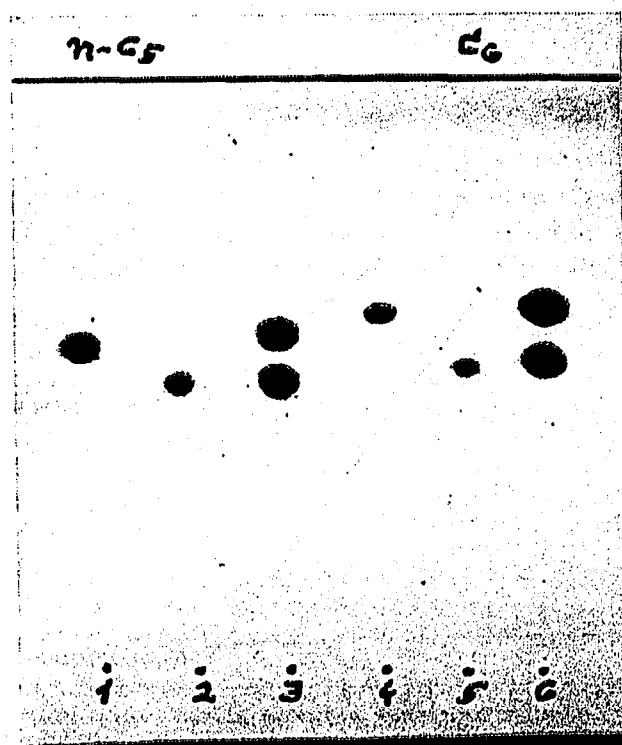


Fig. 3. TLC of liquid valeraldoxime (1), crystalline valeraldoxime (2), mixture of valeraldoximes (3), liquid hexanaloxime (4), crystalline hexanaloxime (5), and mixture of hexanaloximes (6).

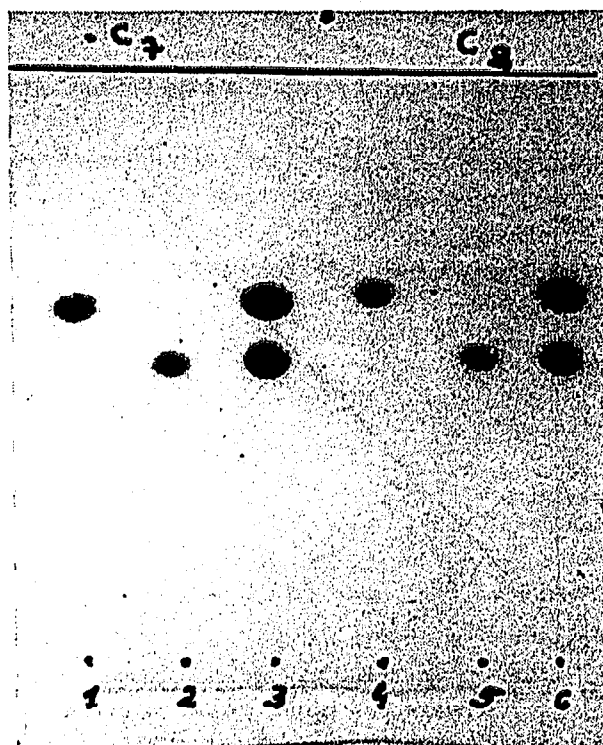


Fig. 4. TLC of liquid heptanaloxime (1), crystalline heptanaloxime (2), mixture of heptanaloximes (3), liquid octanaloxime (4), crystalline octanaloxime (5), and mixture of octanaloximes (6).

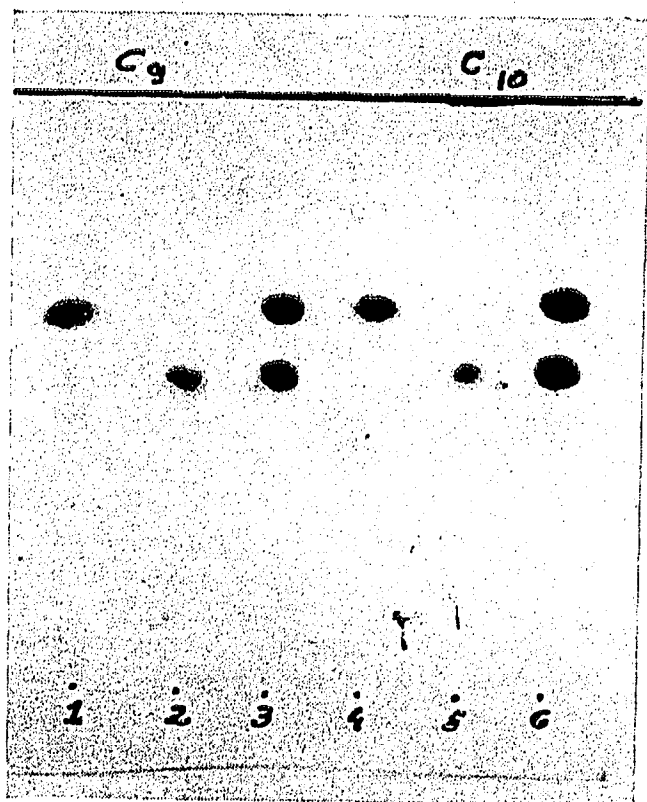


Fig. 5. TLC of liquid nonanaloxime (1), crystalline nonanaloxime (2), mixture of nonanaloximes (3), liquid decanaloxime (4), crystalline decanaloxime (5), and mixture of decanaloximes (6).

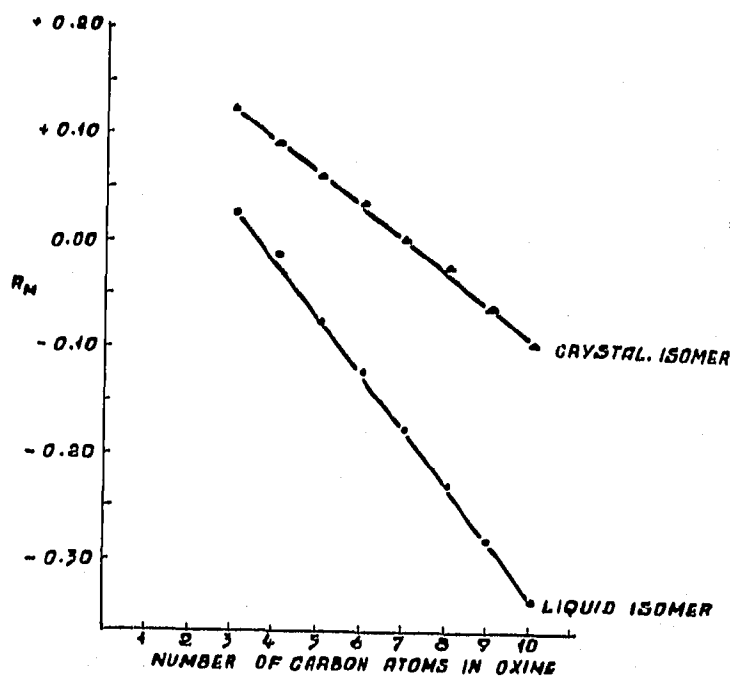
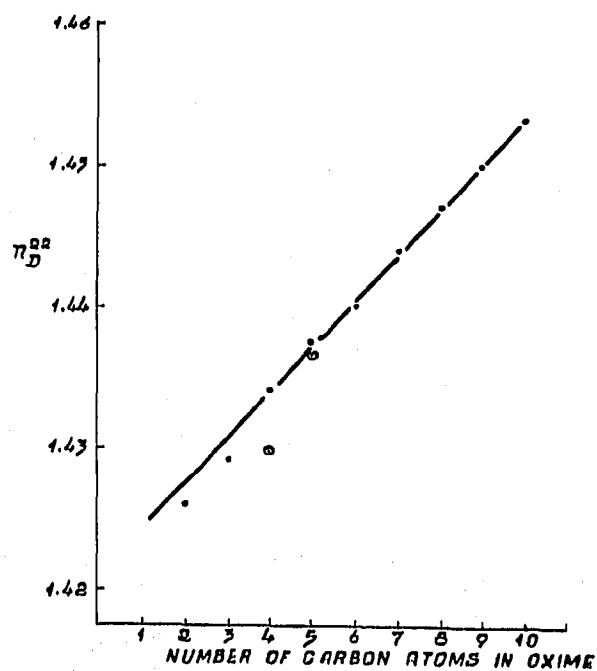


Fig. 6. Refractive indices of liquid isomerides. (●) *n*-aldoximes; (○) iso-aldoximes.

Fig. 7. Graph of R_M values vs. number of carbon atoms for the two series of aliphatic aldoximes.

The above results proved that, unlike hitherto published results, aliphatic aldoximes, from C_2 - C_{10} , could be separated into pure isomerides: liquid and crystalline. On the basis of greater stability, greater adsorption energy and lower mobilities in TLC, the *anti* configuration could be ascribed to the crystalline isomerides, which would also be in conformity with our previous experience in the aromatic series¹². The investigation by PHYLLIPS⁵, who found that the crystalline acet-, propion- and heptanaloximes yielded a single C-H resonance, coincident with that assigned to the *anti* form of the oxime in an equilibrium mixture, also justifies the assumption. By similar arguments the *syn* configuration is ascribed to the liquid isomerides.

In addition we showed that dynamic equilibrium was established sooner or later with both forms of aliphatic aldoximes, regardless of their relative stability. Direct evidence for the kinetics of such a conversion was readily gained by TLC.

Other physical measurements with the separated isomerides will be published in a subsequent paper.

EXPERIMENTAL

Melting points are not corrected.

The aldoximes from C_4 - C_{10} were obtained according to the slightly modified procedure of DUNSTAN AND DYMOND³. To the cold mixture of freshly distilled aldehyde (0.04 mole) and saturated aqueous solution of $NH_2OH \cdot HCl$ (0.04 mole and 10% excess) a concentrated solution of Na_2CO_3 (0.02 mole) was added dropwise with constant stirring. Stirring was continued for a further hour. The oximes from C_4 - C_6 , as well as iso- C_4 and iso- C_6 , were extracted with ether and distilled, and the ones from C_6 - C_{10} , which separated immediately as crude crystalline mass, were recrystallized from alcohol.

Formaldoxime¹³, acetaldoxime¹⁴ and propionaldoxime³ were prepared strictly according to the respective procedures.

All of the aldoximes were separated in the same way: 100 mg of the respective aldoxime was placed on a column of 40 g silica gel (Merck, für Chromatographie, 0.2-0.5 mm), 1.8 cm diameter column, 65 cm, and eluted with petroleum ether (b.p. 40-65°, dried over sodium)-ethyl acetate (50:10, v/v). The flow rate was 2-3 drops

TABLE III
MICROANALYSES OF LIQUID ALDOXIMES

	Calculated			Found		
	C	H	N	C	H	N
Propionaldoxime (C_3H_7ON)	49.30	9.65	19.17	49.02	9.87	18.92
Butyraldoxime (C_4H_9ON)	55.14	10.41	16.08	55.41	10.38	15.96
Iso-butyraldoxime (C_4H_9ON)	55.14	10.41	16.08	54.95	10.67	16.48
Valeraldoxime ($C_5H_{11}ON$)	59.37	10.96	13.85	59.36	10.99	13.55
Iso-valeraldoxime ($C_5H_{11}ON$)	59.37	10.96	13.85	59.52	10.77	13.96
Hexanaloxime ($C_6H_{13}ON$)	62.57	11.38	12.16	62.90	11.44	12.40
Heptanaloxime ($C_7H_{15}ON$)	65.07	11.70	10.84	64.85	11.67	10.64
Octanaloxime ($C_8H_{17}ON$)	67.09	11.96	9.78	66.90	11.82	9.58
Nonanaloxime ($C_9H_{19}ON$)	68.74	12.18	8.90	68.95	12.14	9.13
Decanaloxime ($C_{10}H_{21}ON$)	70.12	12.36	8.18	70.40	12.08	8.24

in 5 sec and the effluent was collected in fractions of 5 ml in test tubes. In each separation approximately 5–6 of the test tubes collected were liquid aldoxime isomeride, 6–7 test tubes a mixture and 7–8 solid isomeride. The eluants, combined on the basis of TLC, were evaporated at normal temperature under reduced pressure and in the case of liquid isomerides immediately measured with an Abbé-refractometer (Carl Zeiss-Jena) and microanalysed.

The monitoring thin-layer chromatography was performed in an identical manner to that described in previous publications¹² with standard 0.2 mm silica gel G chromatoplates in benzene-ethyl acetate (50:10, v/v). Better separation (Figs. 1–5, Table II) was accomplished by running the plate twice to the 14 cm mark in the same mixture with intermittent drying. The entire operation for one development took 45 min and for two, about 2 h. The quantity applied was 10 μ l of 0.1% chloroform solution and the spots were detected by means of iodine or, in the case of acetaldoximes, with an alcoholic solution of AgNO₃.

For reasons discussed above, the microanalysis of liquid acetaldoxime is lacking. The others are given in Table III.

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SUMMARY

It has been demonstrated that in the whole series from acet- to decanaloxime, including iso-butyr- and iso-valeraldoximes, two stereoisomeric forms, a liquid and a solid one, exist. By use of column and thin-layer chromatography both forms were separated and characterized. A "factor of geometrical isomerism" has been calculated on the basis of the mutual relationship between the R_M values of the liquid and solid isomers.

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