E11

Hoechst

Hoechst Aktiengesellschaft
CONSUMER PRODUCTS DIVISION
Research

Stability Test of OCTOPIROX R (PIROCTONE OLAMINE) Substance for 3 Years at Room Temperature

E 12

1.1 Test Sample

Octopirox Substance Lot No.	Manufacturing Date
E 001	Dec. 2, 1975
E 002	Dec. 2, 1975
B 004	Aug. 26, 1977

1.2 Test Period

May 22, 1978 - May 29, 1981
(in 6 months intervals).

1.3 Container

Colorless glass bottles with plastic insert and screw cap.

1.4 Storage Conditions

Storage at room temperature (18 - 26 °C) in a laboratory cabinet.

2 Test Items

2.1 Appearance

2.2 Solution in Methanol

Solution containing 1.0 g of the sample to be tested dissolved in 10 ml of methanol should be colorless or slightly yellowish and clear.

Vorsitzender des Aufsichtsrats Karl Winnacker · Vorstand Rolf Sammet, Vorsitzender; Kurt Lanz stellv. Vorsitzender, Erhard Bouillon, Rudolf Frank, Enrique Hartung, Wolfgang Hilger, Willi Hoerkens, Josef Nowotny, Wolfgang von Pölnitz, Hans Reintges, Jurgen Schaalhausen Hans Schlichter Klaus Weissermel stellv. Mario Fruhauf · Sitz der Gesellschaft Frankfurt am Main · Handelsregister Frankfurt am Main Abt. B Nr. 14500

2.3 UV Spectrum

Dissolve 10 mg of the sample to be tested (after drying at room temperature (20 - 22 °C) and under reduced pressure (10-12 mmHg) above silica gel for 2 hours), accurately weighed, in 0.1 M methanolic sodium hydroxide solution to produce precisely 500 ml. Record an UV spectrum from 360 to 230 nm against the solvent (0.1 M methanolic sodium hydroxide) by using 1 cm cells.

Preparation of 0.1 M methanolic sodium hydroxide:

Dilute an aqueous solution of 4.000 g of sodium hydroxide (= Fixanal, Item No. 382 10, Riedel-de Haën, Seelze-Hannover, Fed. Rep. of Germany) with methanol up to 1000 ml.

Remarks: The recording of the UV spectra and the measurement of the specific extinction (absorbancy) (see test item 2.6) were performed by using the Zeiss UV spectrophotometer Model DM4 equipped with the BBC/Goerz recorder Model SERVOGOR 210.

Rate of wave-length: 30 nm/min; rate of paper feed: 30 nm/min.

The reason for using 0.1 M methanolic sodium hydroxide instead of methanol as solvent is the finding that in this medium the site of the absorption maximum at 317 nm and the absorbancy of Octopirox are readily reproducible in contrast to solutions in methanol where the site of the absorption maximum at about 304 nm and the absorbancy depend to some extent on the quality of the methanol used.

2.4 IR Spectrum

Compact a homogenous mixture of about 1.2 ± 0.1 mg of the sample to be tested and about 250 mg of potassium bromide and record an IR spectrum from the wave number 400 to 4000 cm^{-1}.

Remark: The recording of the IR spectra was carried out by using the Perkin-Elmer IR spectrophotometer Model 377; Time: 13 min; Slit: N.

2.5 Thin Layer Chromatography

Mobile phase No. 1	Dioxane	10 % (v/v)
	0.2 M Disodium Edetate Solution	40
	Methanol	40
	Methyl Ethyl Ketone	5
	Ethanolamine	5

Mobile phase No. 2	Methanol	75 % (v/v)
	Isopropanol	20
	28 % Aqueous Ammonia	5
Mobile phase No. 3	n-Butyl Acetate	60 % (v/v)
	Ethanol	30
	Water	10

Stationary phase: Pre-coated TLC glass plates, type polyamide 11 F_{254} (Merck, Darmstadt, Fed. Rep. of Germany).

Plates are pre-activated for 1 hour at 110 °C before use.

Quantities applied:

A) 10 µl of a solution of the sample to be tested (1 % w/v in methanol).

B) 10 µl of a solution of Octopirox standard substance (1 % w/v in methanol).

Distance from start to solvent front: approximately 10 cm.

Detection: UV (254 nm).

Evaluation: The spots from samples A and B should show the same R_f value in all three mobile phases. From sample A, no other spot must be detected.

0.2 M Disodium Edetate Solution:

74.448 g disodium edetate dihydrate and 10 g sodium hydroxide are dissolved in water up to 1000 ml (e.g. = Idranal III, Riedel-de Haën, Seelze-Hannover, Fed. Rep. of Germany, or Titriplex III, Merck, Darmstadt, Fed. Rep. of Germany).

2.6 Absorbance in 0.1 M methanolic sodium hydroxide at 317 nm

Measure the absorbance (A_T) at the absorption maximum (317 nm) of the solution obtained according to the procedure described under 2.3 against the solvent by using 1 cm cells.

$$\text{Absorbancy } E^{1\,\%}_{1\,cm} = \frac{5000 \cdot A_T}{\text{weight of sample (mg)}}$$

The $E^{1\,\%}_{1\,cm}$ value should be 225 ± 5 %.

2.7 Loss on drying

Dry 1 g of the sample to be tested, accurately weighed, at room temperature (20 - 22 °C) and under reduced pressure (10 - 12 mmHg) above silica gel for 2 hours and determine gravimetrically the loss of quantity.

2.8 Assay

Weigh accurately 150 mg of the sample to be tested, dissolve in 35 ml of dimethylformamide and titrate with 0.1 M Lithium Methoxide Volumetric Solution in a nitrogen atmosphere. Indicator: 3 drops of Thymol blue, color change from yellow to blue.

By using the same method perform the blank test for adjustment. 1 ml of 0.1 M Lithium Methoxide Volumetric Solution is equivalent to 29.848 mg of Octopirox ($C_{16}H_{30}N_2O_3$).

Preparation of 0.1 M Lithium Methoxide Volumetric Solution: Previously according to BP 73 and later according to BP 80.

Indicator: 0.3 % Solution of Thymol blue in dimethylformamide.

3 Results

The stability test results are specified in Appendices 1 - 3.

Appendix 4 shows the UV Spectrum Chart No. A1 of Lot No. E 001.

Appendix 5 shows the UV Spectrum Chart No. A7 of Lot No. E 001.

Appendix 6 shows the IR Spectra Chart No. B1 and Chart No. B7 of Lot No. E 001.

Appendix 7 shows the TLC Photos No. 1 - 3 of
Octopirox Standard
Lot No. E 001
Lot No. E 002
Lot No. B 004

Appendix 8 shows the TLC Photos No. 4 - 6 of
Octopirox Standard
Lot No. E 001
Lot No. E 002
Lot No. B 004

Appendix 9 shows the UV Spectrum Chart No. A1 of Lot No. E 002.

Appendix 10 shows the UV Spectrum Chart No. A7 of Lot No. E 002.

Appendix 11 shows the IR Spectra Chart No. B1 and Chart No. B7 of Lot No. E 002.

Appendix 12 shows the UV Spectrum Chart No. A1 of Lot No. B 004.

Appendix 13 shows the UV Spectrum Chart No. A7 of Lot No. B 004.

Appendix 14 shows the IR Spectra Chart No. B1 and Chart No. B7 of Lot No. B 004.

4 Conclusion

The results shown in Appendices 1 - 14 demonstrate no evidence of instability or decomposition of the Octopirox substance over a period of three years' storage at room temperature.

Frankfurt (Main),
July 30, 1981

CONSUMER PRODUCTS DIVISION
Research

(Dr. E. Futterer)

Appendices 1 - 14

Stability Test Results of Octopirox at Room Temperature

Lot No. E 001

Test Items		No.	Initial	6 months	12 months	18 months	24 months	30 months	36 months
Appearance		1	White to faint yellow	no change	no change	no change	no change	no change	no change
		2	White to faint yellow	no change	no change	no change	no change	no change	no change
		3	White to faint yellow	no change	no change	no change	no change	no change	no change
Solubility Methanol		1	Clear, slightly yellow	no change	no change	no change	no change	no change	no change
		2	Clear, slightly yellow	no change	no change	no change	no change	no change	no change
		3	Clear, slightly yellow	no change	no change	no change	no change	no change	no change
UV Spectrum		1	Chart No. A1	no change	no change	no change	no change	no change	Chart No.A7
IR Spectrum		1	Chart No. B1	no change	no change	no change	no change	no change	Chart No.B7
TLC	Mobile Phase No. 1	1	One spot Photo No. 1	no change	no change	no change	no change	no change	One spot Photo No. 4
	No. 2	1	One spot Photo No. 2	no change	no change	no change	no change	no change	One Spot Photo No. 5
	No. 3	1	One spot Photo No. 3	no change	no change	no change	no change	no change	One spot Photo No. 6
Absorbance, $E^{1\%}_{1cm}$ (317 nm)		1	229	230	228	229	226	228	227
		2	226	229	230	226	228	227	228
		3	226	226	229	230	226	228	227
Loss on Drying (%)		1	0.01	0.01	0.01	0.02	0.02	0.02	0.02
		2	0.02	0.02	0.03	0.02	0.01	0.01	0.03
		3	0.01	0.02	0.02	0.01	0.02	0.03	0.02
Assay (%)		1	100.0	99.9	99.9	99.8	100.1	100.0	99.9
		2	99.9	100.1	99.8	99.9	100.1	99.8	100.2
		3	99.9	99.8	100.0	99.9	99.9	99.9	99.8

Stability Test Results of Octopirox at Room Temperature

Lot No. E 002

Test Items		No.	Initial	6 months	12 months	18 months	24 months	30 months	36 months
Appearance		1	White to faint yellow	no change	no change	no change	no change	no change	no change
		2	White to faint yellow	no change	no change	no change	no change	no change	no change
		3	White to faint yellow	no change	no change	no change	no change	no change	no change
Solubility Methanol		1	Clear, slightly yellow	no change	no change	no change	no change	no change	no change
		2	Clear, slightly yellow	no change	no change	no change	no change	no change	no change
		3	Clear, slightly yellow	no change	no change	no change	no change	no change	no change
UV Spectrum		1	Chart No. A1	no change	no change	no change	no change	no change	Chart No. A7
IR Spectrum		1	Chart No. B1	no change	no change	no change	no change	no change	Chart No. B7
TLC	Mobile Phase No. 1	1	One spot Photo No. 1	no change	no change	no change	no change	no change	One spot Photo No. 4
	No. 2	1	One spot Photo No. 2	no change	no change	no change	no change	no change	One spot Photo No. 5
	No. 3	1	One spot Photo No. 3	no change	no change	no change	no change	no change	One spot Photo No. 6
Absorbance, $E^{1\%}_{1cm}$ (317 nm)		1	226	228	229	227	228	229	228
		2	228	229	230	228	228	227	227
		3	226	229	229	230	227	228	228
Loss on Drying (%)		1	0.01	0.02	0.02	0.01	0.03	0.02	0.03
		2	0.01	0.01	0.03	0.02	0.01	0.02	0.01
		3	0.03	0.01	0.01	0.02	0.01	0.02	0.01
Assay (%)		1	99.8	99.9	99.9	100.1	99.9	99.9	99.8
		2	99.9	99.9	99.8	99.9	99.8	99.9	99.9
		3	99.9	100.0	99.9	99.8	99.8	99.8	99.7

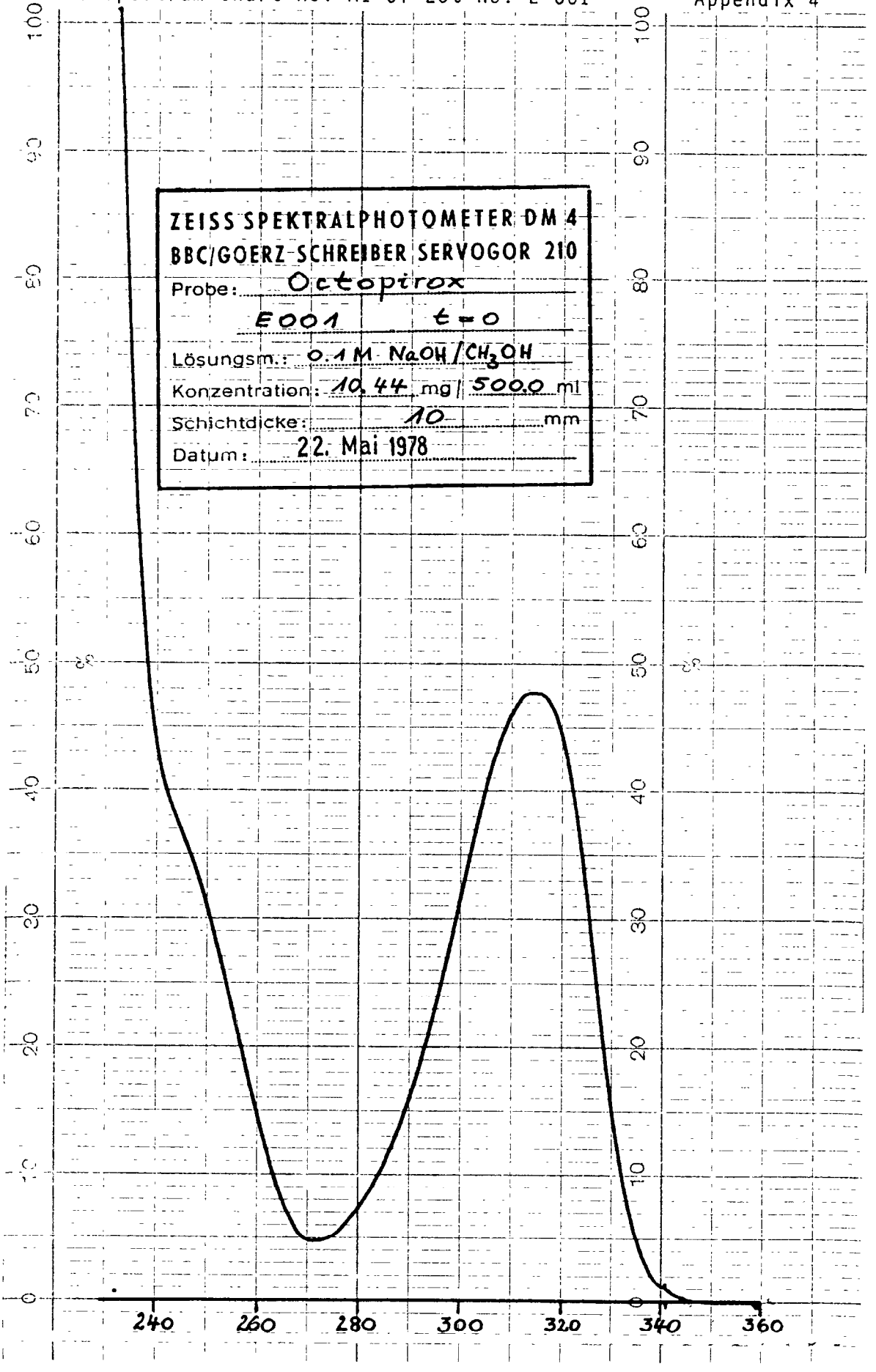
Stability Test Results of Octopirox at Room Temperature

Lot No. B 004

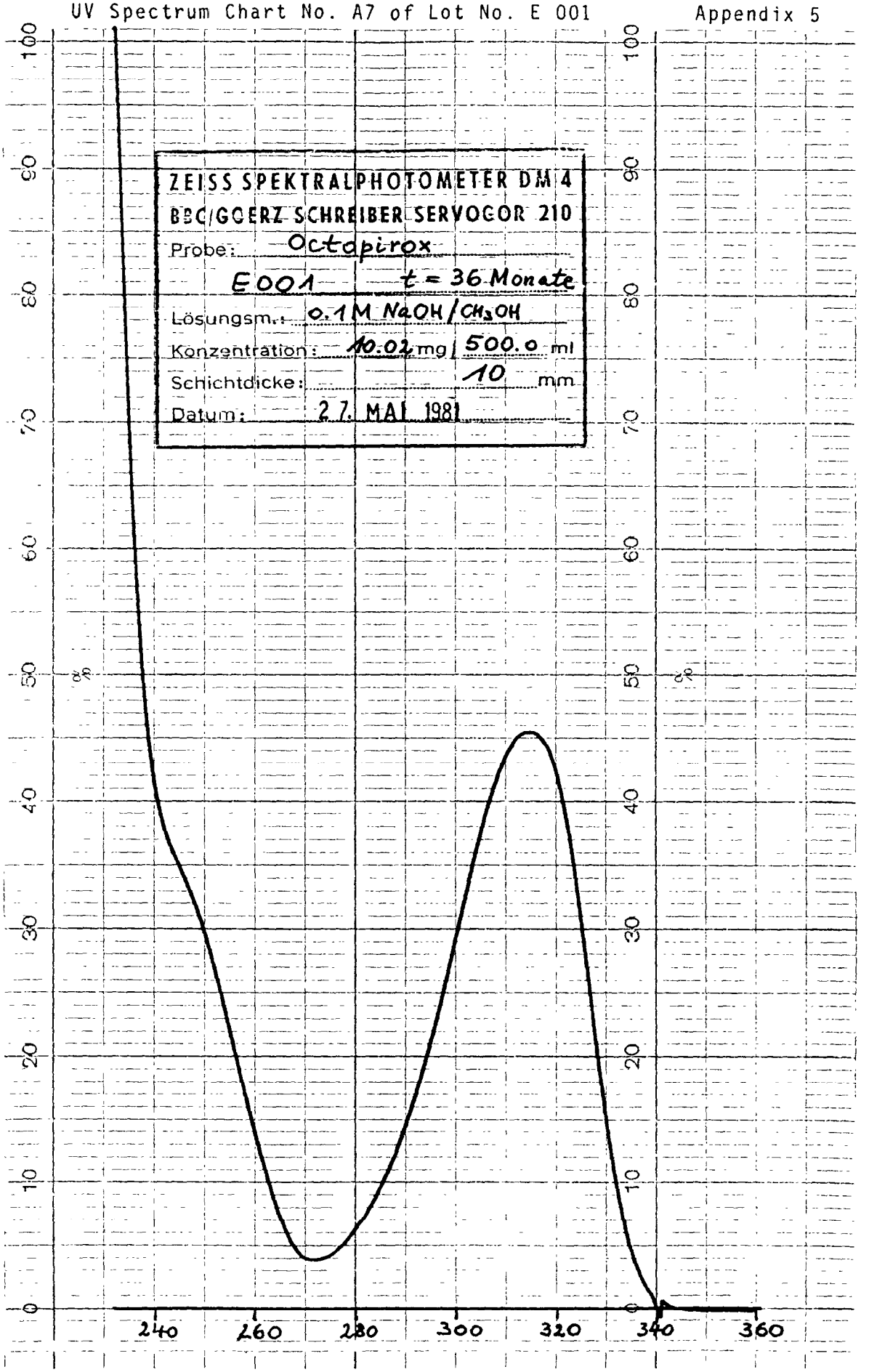
Test Items		Interval / No.	Initial	6 months	12 months	18 months	24 months	30 months	36 months
Appearance		1	White to faint yellow	no change	no change	no change	no change	no change	no change
		2	White to faint yellow	no change	no change	no change	no change	no change	no change
		3	White to faint yellow	no change	no change	no change	no change	no change	no change
Solubility Methanol		1	Clear, slightly yellow	no change	no change	no change	no change	no change	no change
		2	Clear, slightly yellow	no change	no change	no change	no change	no change	no change
		3	Clear, slightly yellow	no change	no change	no change	no change	no change	no change
UV Spectrum		1	Chart No. A1	no change	no change	no change	no change	no change	Chart No. A7
IR Spectrum		1	Chart No. B1	no change	no change	no change	no change	no change	Chart No. B7
TLC	Mobile Phase No. 1	1	One spot Photo No. 1	no change	no change	no change	no change	no change	One spot Photo No. 4
	No. 2	1	One spot Photo No. 2	no change	no change	no change	no change	no change	One spot Photo No. 5
	No. 3	1	One spot Photo No. 3	no change	no change	no change	no change	no change	One spot Photo No. 6
Absorbance, $E^{1\%}_{1cm}$ (317 nm)		1	226	227	225	226	225	227	225
		2	225	226	227	225	228	229	226
		3	224	225	225	226	227	226	226
Loss on Drying (%)		1	0.01	0.02	0.01	0.03	0.02	0.03	0.02
		2	0.02	0.02	0.01	0.01	0.02	0.01	0.02
		3	0.02	0.03	0.02	0.02	0.01	0.02	0.02
Assay (%)		1	99.8	99.9	99.8	99.9	99.8	99.9	99.8
		2	99.7	99.8	99.9	99.7	99.8	99.7	99.8
		3	99.9	99.8	99.8	99.8	99.7	99.8	99.7

UV Spectrum Chart No. A1 of Lot No. E 001

Appendix 4



UV Spectrum Chart No. A7 of Lot No. E 001 Appendix 5



IR Spectra of Octopirox / Initial: Chart No. B1
of Lot No. E 001 after 3 Years' Storage at RT: Chart No. B7

Chart No. B1

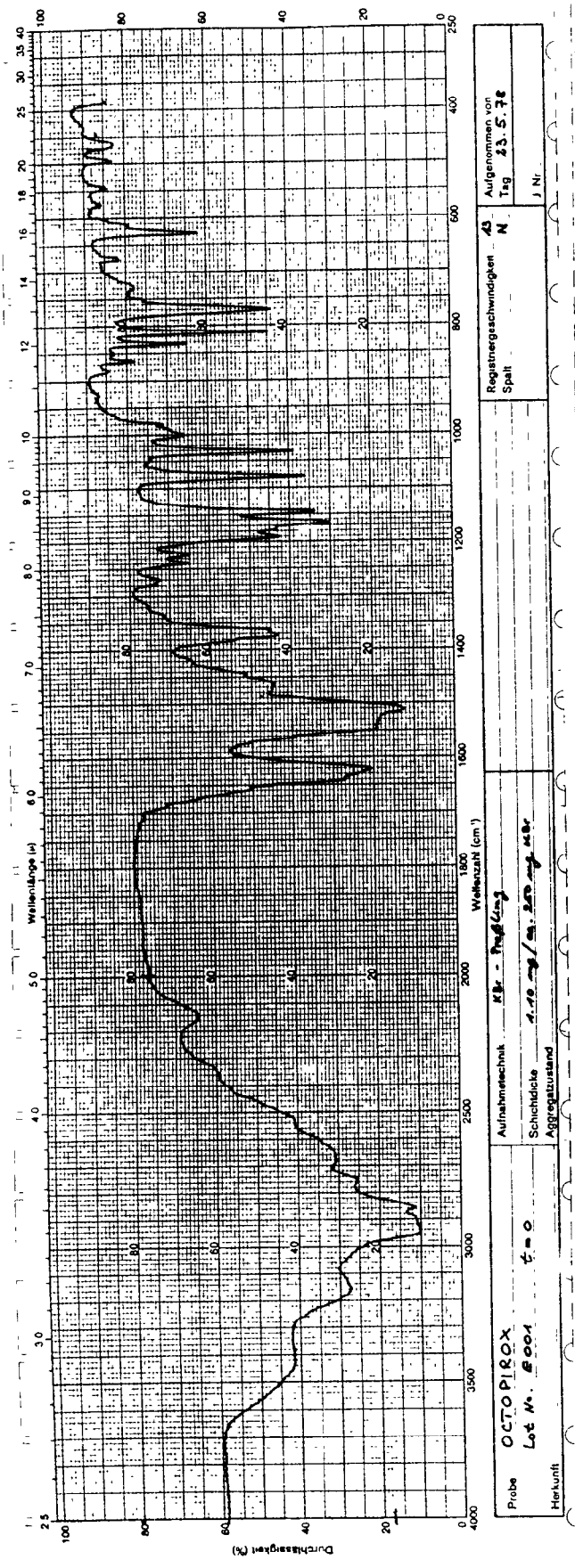
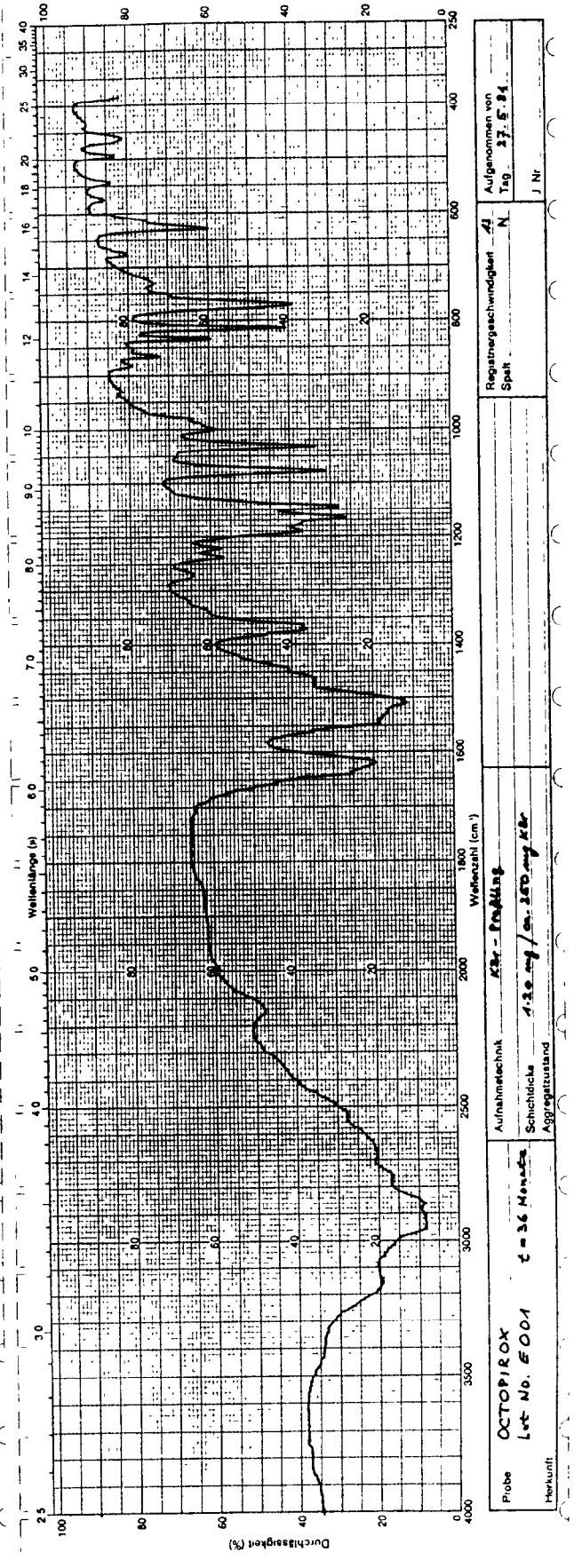


Chart No. B7



Photos of TLC spots of Octopirox / Initial Value

Mobile Phase No. 1
(Photo No. 1)

Mobile Phase No. 2
(Photo No. 2)

Mobile Phase No. 3
(Photo No. 3)

Standard

Lot No. E 001

Lot No. E 002

Lot No. B 004

Photos of TLC spots of Octopirox
after 3 Years' Storage at Room Temperature

Mobile Phase No. 1
(Photo No. 4)

Mobile Phase No. 2
(Photo No. 5)

Mobile Phase No. 3
(Photo No. 6)

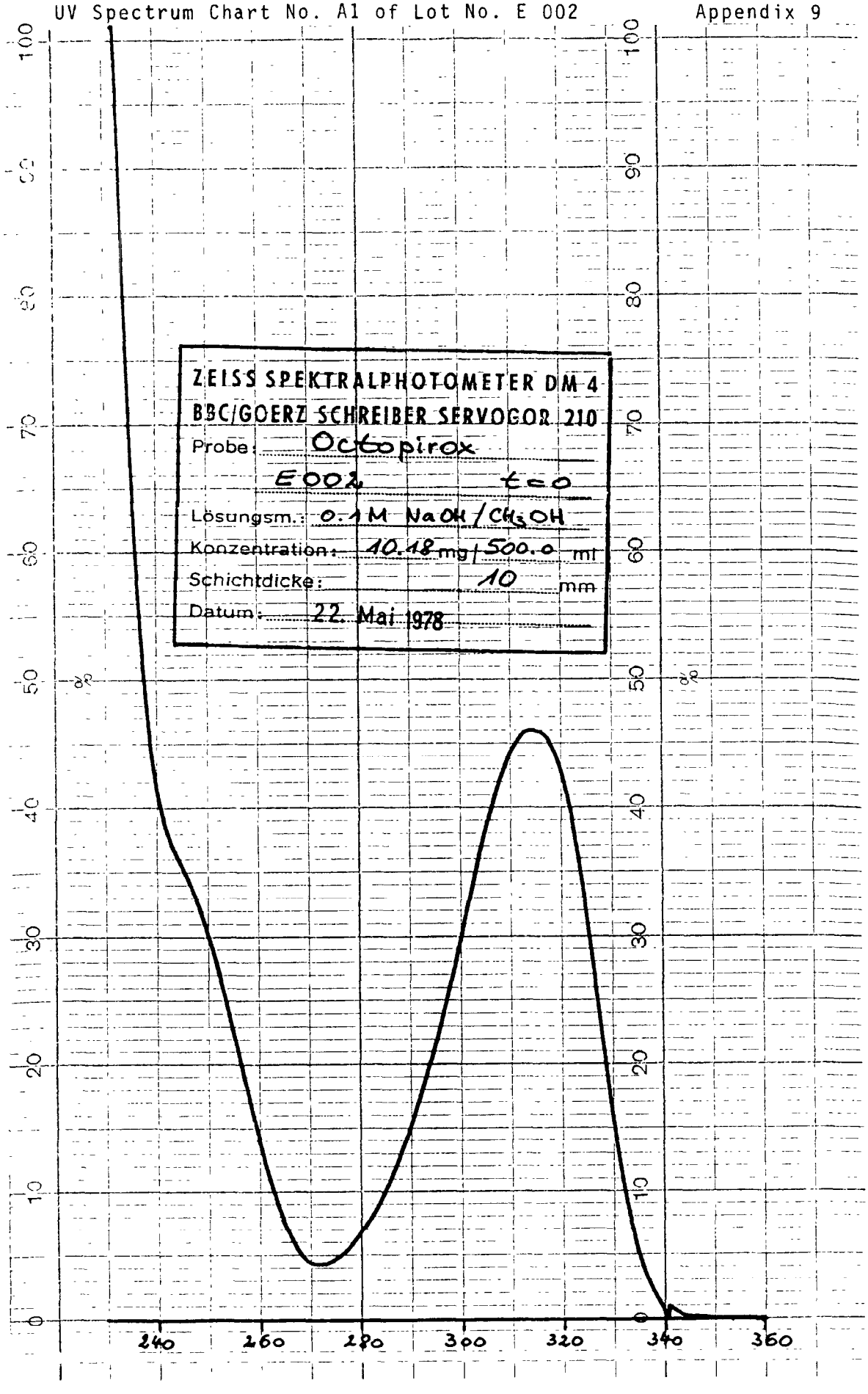
Standard

Lot No. E 001

Lot No. E 002

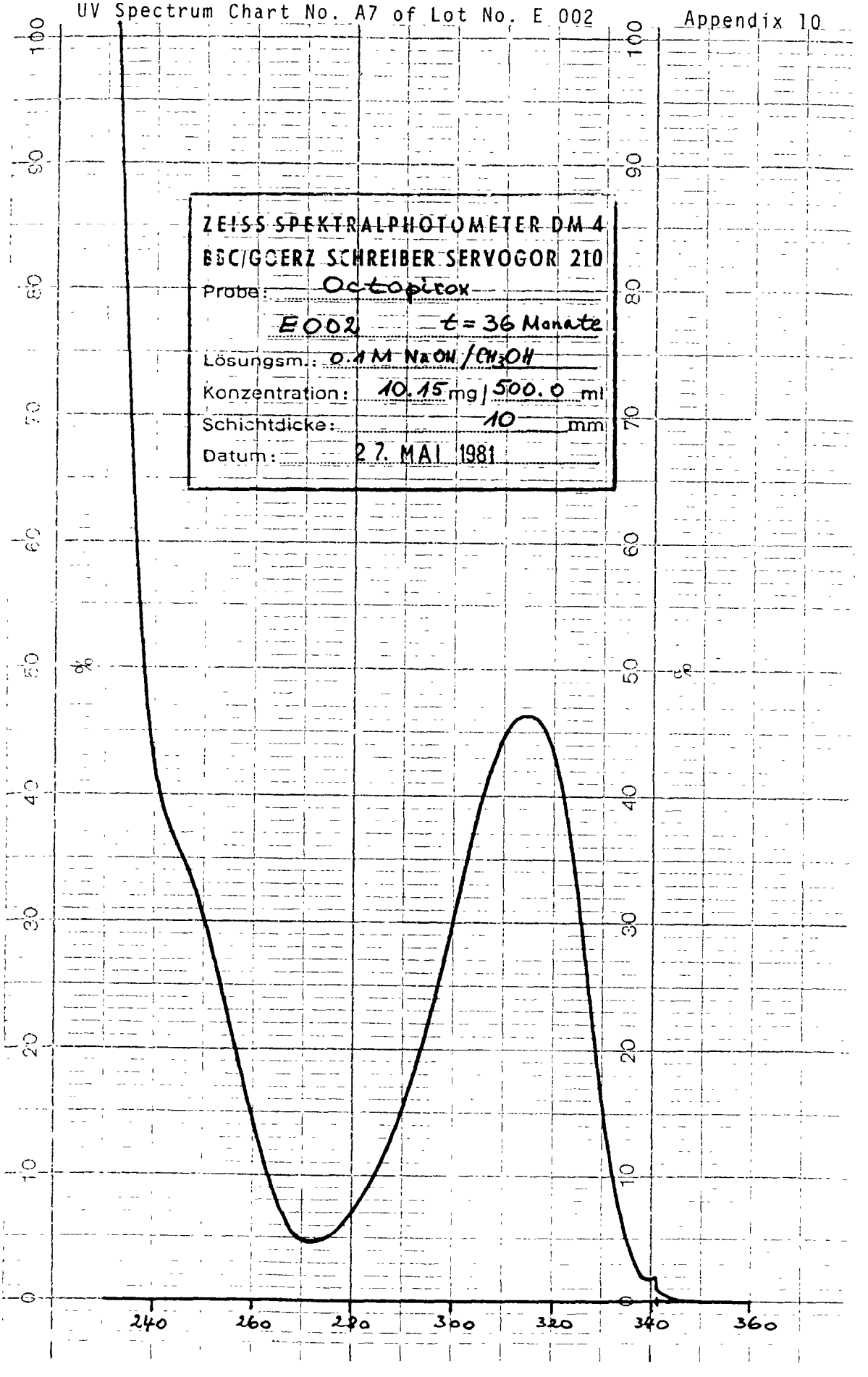
Lot No. B 004

UV Spectrum Chart No. A1 of Lot No. E 002 Appendix 9



UV Spectrum Chart No. A7 of Lot No. E 002

Appendix 10



IR Spectra of Octopirox / Initial: Chart No. B1
of Lot No. E 002 after 3 Years' Storage at RT: Chart No. B7

Chart No. B1

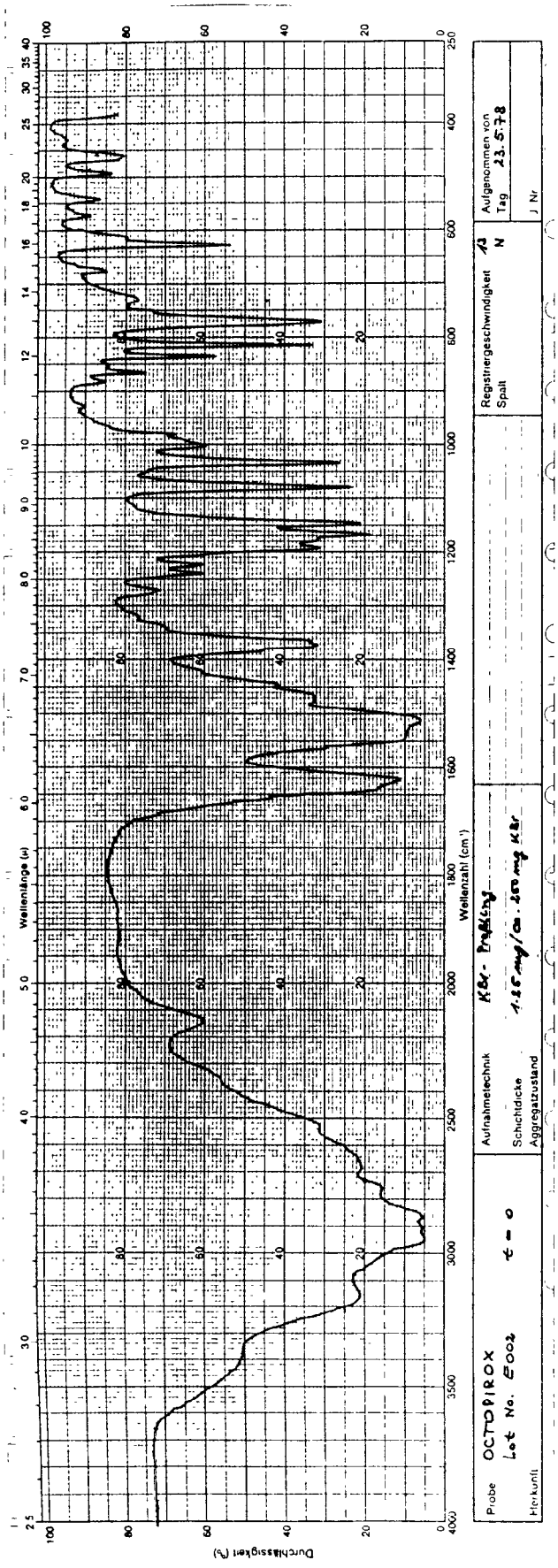
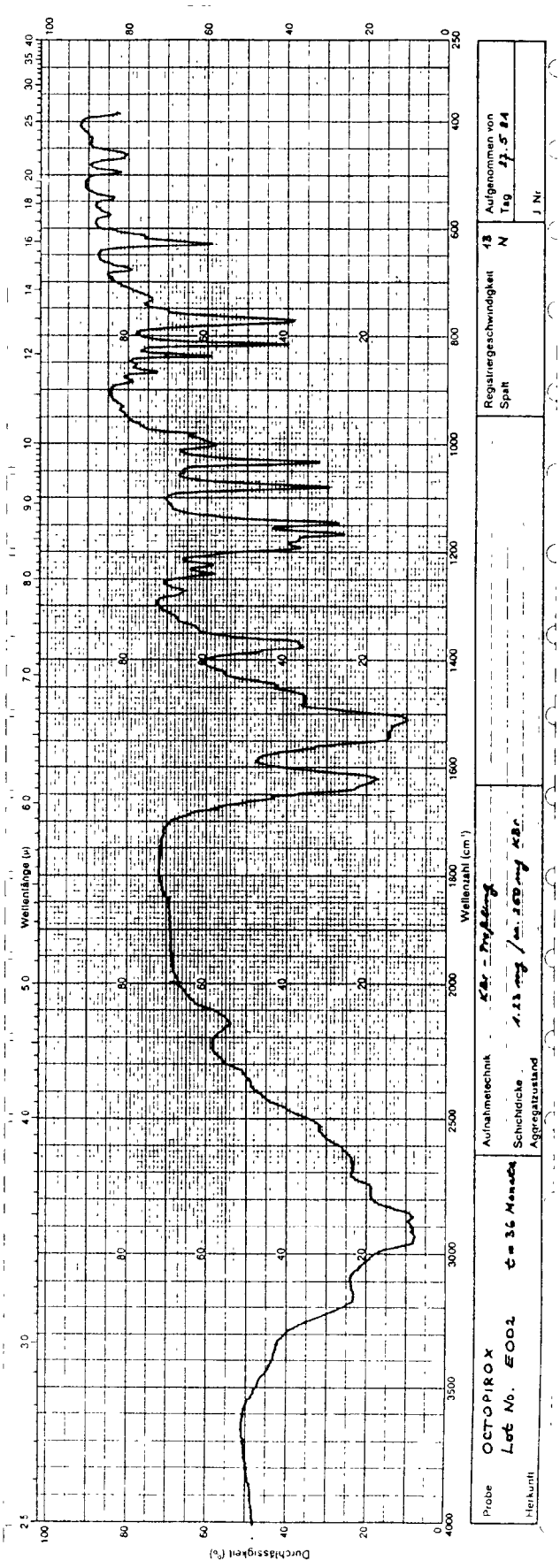
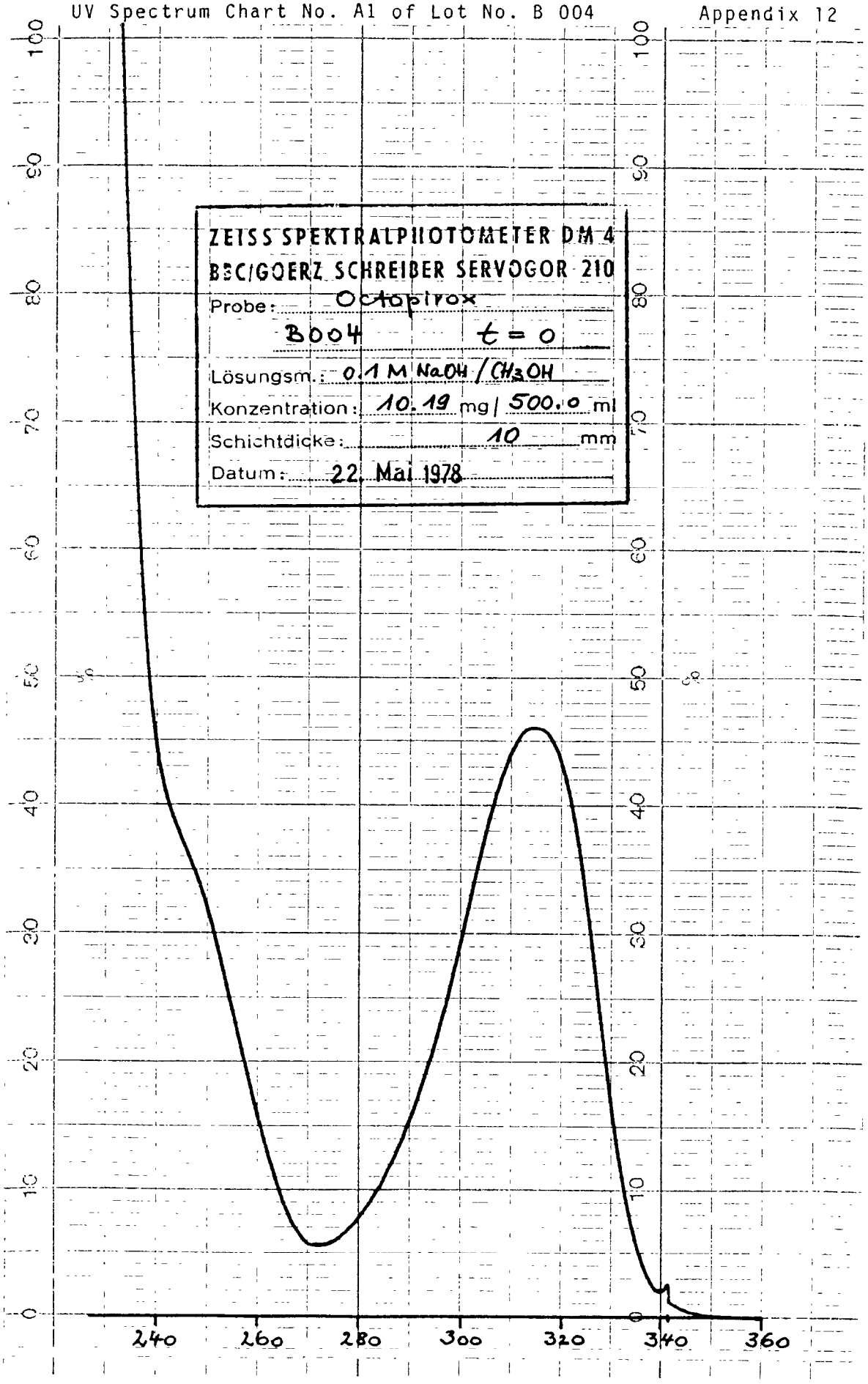


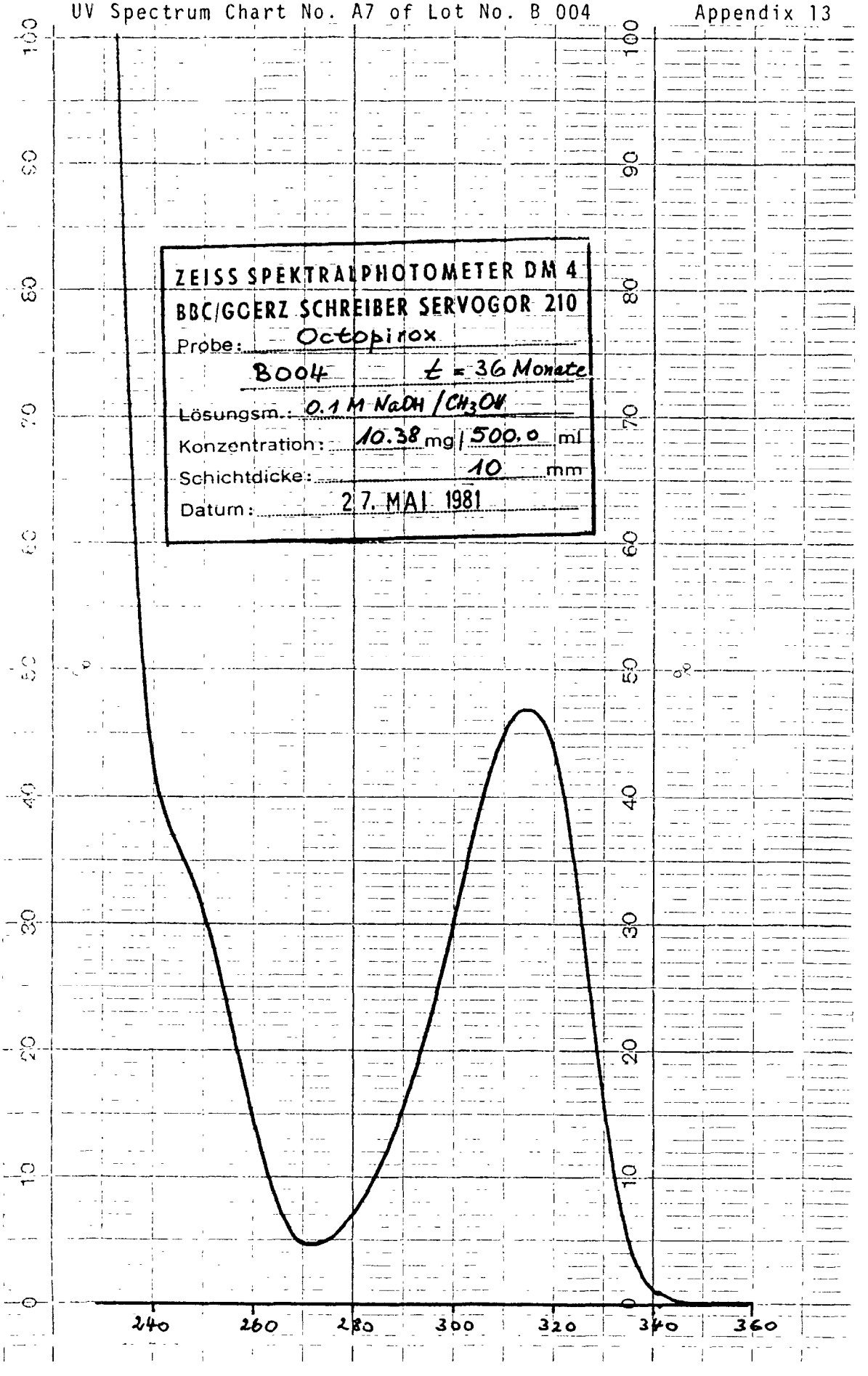
Chart No. B7



UV Spectrum Chart No. A1 of Lot No. B 004 Appendix 12



UV Spectrum Chart No. A7 of Lot No. B 004 Appendix 13



IR Spectra of Octopirox / Initial: Chart No. B1
of Lot No. B 004 after 3 Years' Storage at RT: Chart No. B7

Chart No. B1

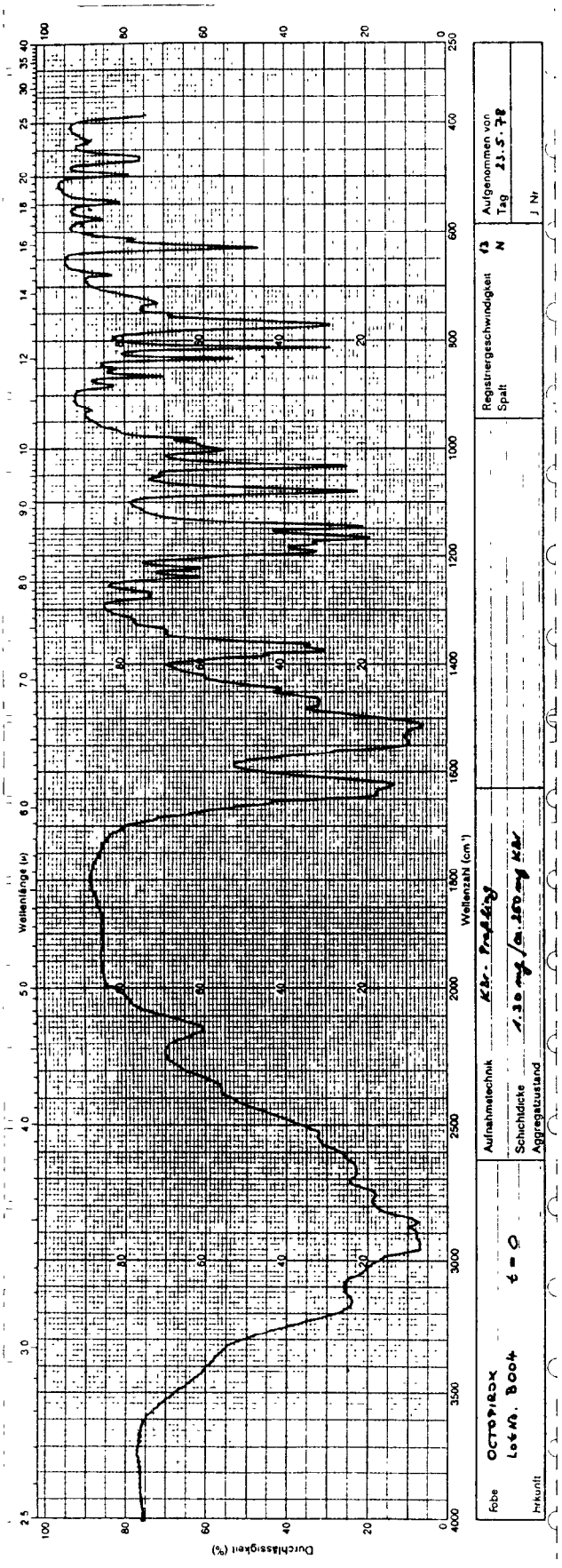
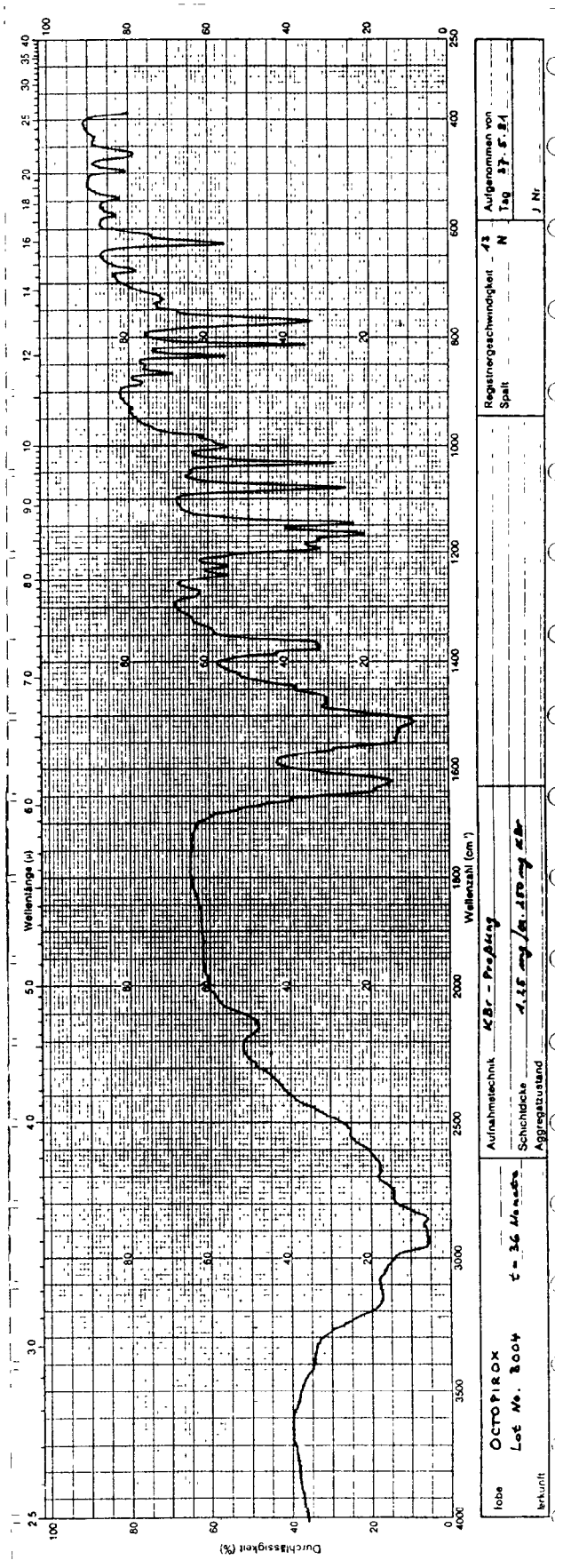



Chart No. B7