Chemistry. — *On the Preparation of β-Phenyl-isopropylamine (Benzedrine), of the isomeric α-Phenyl-propylamine and of β-Phenyl-α-propylenediamine and on the Resolution of these Bases into their Optically-active Antipodes* I. By F. M. JAEGER and J. A. VAN DIJK.

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§ 1. For the purpose of executing some investigations, the results of which will later be communicated, we had to prepare greater quantities of the bases *β-phenyl-isopropylamine*: $C_6H_5 . CH_2 . CH(NH_2) . CH_3$ (*benzedrine*) and its isomeride: *α-phenyl-propylamine*: $C_6H_5 . CH(NH_2) . CH_2 . CH_3$, both in the racemic and in the optically-active forms; as well as of the hitherto unknown diamine: *β-phenyl-α-propylenediamine*: $C_6H_5 . CH(NH_2) . CH(NH_2) . CH_3$, which by the presence of two asymmetrical carbon-atoms within its molecule should exist in two racemic and four optically-active forms. The two *mono*amines mentioned which are closely related to the physiologically active *ephedrine*-bases, have already formerly been prepared [1]), although the second in only a rather incompletely pure state. In the present paper we wish, as a preliminary introduction to the later experiments, to publish the results of the preparative methods followed and of the resolution of the *benzedrine* thus obtained into its optically-active components.

Benzedrine was prepared by us, starting from *methylbenzylcetone* (boilingpoint: 76° C. under a pressure of 3 m.M.), this being transformed into *methylbenzylcetoxime* (meltingpoint: 68°,5 C.) and the latter being subsequently reduced in absolute alcoholic solution by means of a 8- or 10-fold excess of sodium, in the way previously described [2]).

The pure *methylbenzylcetone* is a colourless liquid which, contradictory to the data given in the literature (+ 27° C.), proved to crystallize at —16° C. with a very small velocity of crystallization and only after inoculation with a nucleus of the solidified substance. We never were able to find a higher temperature of crystallization than this, although the accompanying heat-effect appeared to be rather considerable.

The corresponding *cetoxime*: $C_6H_5 . CH_2 . (C:NOH) . CH_3$ was prepared by treatment of the *cetone* with a 10 % excess of free hydroxylamine in methyl-alcoholic solution at room-temperature. It shows an

[1]) W. LEITHE, Ber. d. d. chem. Ges., **65**, 660 (1932) F. P. NABERHAUER, Eng. Pat., ref. Chem. Zentral Blatt (1937), I, 662; P. BILLON, Compt. rend. Paris, **182**, 472 (1926).

[2]) F. M. JAEGER and J. A. VAN DIJK, Proceed. R. Neth. Acad. of Sciences Amst., **39**, 384, 392 (1936).

enormous tendency to crystallization, although the rate of the latter is also only small; the *cetoxime* can easily be obtained from a solution in ethyl-acetate + absolute alcohol in very big prismatic crystals, which often show a thickness of several centimeters (Conf. § 2).

On reduction of the *cetoxime* by means of an excess of sodium in a boiling absolute alcoholic solution in the way previously [2]) described, the yield of the amine obtained proved to be *considerably higher* than that mentioned in the literature, — the base there having been obtained by means of *electrolytical* reduction: we here often obtained 90—95 % of the theoretically calculated quantity [3]).

The free and thoroughly dried base then was destilled in vacuo: the boilingpoint was 63°—64° C. under 7 m.M. pressure; under 1 atmosphere it is 205° C. The racemic *benzedrine* is a very volatile, strongly refracting liquid, with a very bitter and intensively burning taste and a specific weight of 0,9370 at 18° C., — somewhat higher than that of the optically-active components. Its refractive index is 1,550 for sodium-light, — this also being slightly higher than that of the antipodes. In a bath of solid carbonic acid and ethylalcohol the base gets glassy and then extremely slowly starts crystallizing: its meltingpoint is certainly appreciably lower than that of the antipodes. Most probably the racemic liquid base is really a mixture of the two components and *no* true racemic compound.

§ 2. As to the crystallographical characteristics of the *benzylmethyl-cetoxime* mentioned above, the following data were collected.

Benzylmethylcetoxime: $C_6H_5 . CH_2 . C(:NOH) . CH_3$, meltingpoint: 68°—68°.5 C. crystallizes from a solution in ligroine in big, transparent, hexagonally-bounded, tabular crystals or in thin, parallelogram-shaped tables which on {001} show a subdivision in sectors and a fine striation, parallel to the boundaries of the latter. (Fig. 1).

From ethylacetate enormous crystals can be obtained, often several c.M.
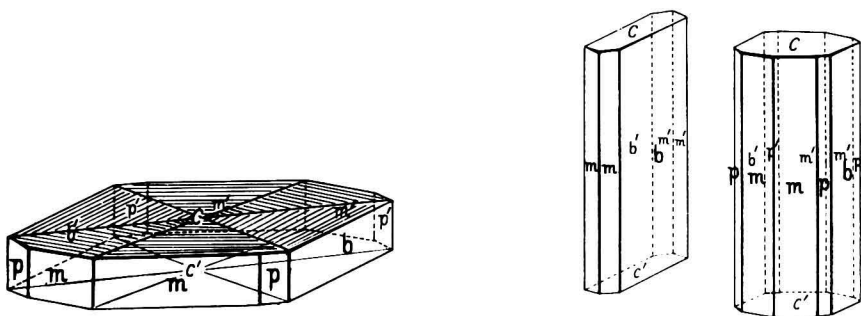
a. Crystals from ligroine.　　　b. Crystals from ethyl-acetate.

Fig. 1. Benzylmethylcetoxime. (68°,5 C.).

[3]) NABERHAUER, for instance, indicates a yield of about only 60% of the theoretical one.

thick, in the form of prisms, but *without* other terminal faces than {001}. They are very plastic and, therefore, as a consequence of mechanical deformation they manifest considerable oscillations of their angular values; their deformation takes place along certain glidingplanes of the vertical zone. Because of this fact the crystal-measurements are only approximative.

The forms observed are: $m = \{110\}$ broad and lustrous; $p = \{120\}$, narrow, but yielding good reflexions; $b = \{010\}$, sharply reflecting, well developed, although mostly narrower than m; $c = \{001\}$, very lustrous. The faces of c and of p are often finely striated parallel to the c-axis.

Although pseudo-rhombic, the crystals truly are *monoclinic-prismatic* with: $a : b = 0,55 : 1$ and $\beta = 89°32'$. From the X-ray-examinations, the true parameters appear to be:

$$a : b : c = 0,522 : 1 : 0,3287;$$

$$\text{with } \beta = 89°32'.$$

The angular values are:
$$m : m = (110) : (1\bar{1}0) = 55°8'$$
$$m : p = (110) : (120) = 18 \ 40$$
$$p : b = (010) : (120) = 43 \ 46$$
$$p : c = (120) : (001) = 89 \ 40\tfrac{1}{2}$$
$$m : c = (110) : (001) = 89 \ 36$$

A good cleavability occurs parallel to {010}.

The plane of the optical axes is {010}; the exit of one of the axes is visible on {001}. On {010} the extinction is oblique, with an inclination of 51° with respect to the a-axis. The density was found $= 1,23$ at 20° C.; from the X-ray-data, $d_0 = 1,255$, with $Z = four$ molecules in the elementary cell.

From rotation-spectrograms (with Fe-radiation: $\lambda_\alpha = 1,934$ Å), the dimensions of the elementary cell proved to be: $a_0 = 8,65^5$ Å; $b_0 = 16,58$ Å; $c_0 = 5,458$ Å. A series of SAUTER-spectrograms round the three principal axes gave, for instance, the following reflexions (the triplets in italics correspond to the most intensive images):

1. Round the a-axis:

—	—	(020)	—	(040)	—	
(001)	*(011)*	—	*(031)*	*(041)*	(051)	
(002)	*(012)*	—	(032)	*(042)*	—	

2. Round the c-axis:

—	—	(020)	—	(040)	—	—
—	(110)	*(120)*	*(130)*	*(140)*	(150)	—
(200)	*(210)*	(220)	*(230)*	(240)	(250)	(260)

Several of these indices-triplets are also found in the powder-spectrograms: thus (120), (011), (200), (040), (210), (031), (220), (140), (041), (150), (240), (051), (012) and (250).

As the density of the crystals was determined at 1,21 (20° C.), the elementary cell contains the mass of *4* molecules; the density then calculated is: $d_0 = 1,255$.

No of Line	Distance $2l$ in mM:	Intens:	θ:	$\sin^2 \theta$: (observed)	$\sin^2 \theta$: (calculated)	Indices:

TABLE I. Powder-Spectrogram of Benzylmethylcetoxime (68°,5 C).

No of Line	Distance $2l$ in mM:	Intens:	θ:	$\sin^2 \theta$: (observed)	$\sin^2 \theta$: (calculated)	Indices:
1	36.80	7	9° 13′	0.0257	0.0261	(120)
2	38.42 (β)	2	9 38	0.0280	0.0290	(011) (β)
3	42.70	9	10 42	0.0345	0.0348	(011) (α)
4	49.30	6	12 38	0.0478	0.0476	($\bar{1}$11)
5	51.58 (β)	4	12 55	0.0500	0.0500	(200)
6	54.16	8	13 34	0.0550	⎰ 0.0544 ⎱ 0.0534	(040) . (210)
7	57.38	8	14 22	0.0616	⎰ 0.0620 ⎱ 0.0636	(031) . (220)
8	59.70	5	14 57	0.0665	0.0669	(140) or (131) (β)
9	62.70	10	15 42	0.0732	0.0741	(131) (α)
10	64.44 (β)	3	16 8	0.0772	0.0780	(041) (β)
11	68.04	3	17 2	0.0858	0.0858	($\bar{2}$11) . (041) (α)
12	69.86	6	17 30	0.0904	0.0941	(221)
13	72.58	4	18 11	0.0974	⎰ 0.0958 ⎱ 0.0975	($\bar{2}$21) . (150)
14	76.32	6	19 7	0.1072	0.1044	(240)
15	79.00	1	19 47	0.1146	⎰ 0.1157 ⎱ 0.1163	(310) . (051)
16	83.82	1	20 59	0.1282	0.1289	(012)
17	85.56	1	21 25	0.1333	⎰ 0.1333 ⎱ 0.1362	(250) . (102) . (241)
18	87.50	4	21 55	0.1393	0.1392	(022)
19	90.76	1	22 43	0.1491	0.1509	(122)
20	95.40	2	23 53	0.1639	⎰ 0.1679 ⎱ 0.1666	(132) . (070)
21	97.62	2	24 27	0.1713	⎰ 0.1723 ⎱ 0.1740	(260) . (202)
22	100.50	1	25 10	0.1808	0.1812	($\bar{2}$12)
23	103.30	1	25 52	0.1903	⎰ 0.1917 ⎱ 0.1904	(142) . (222)
24	106.18	2	26 35	0 2003	⎰ 0.1997 ⎱ 0.2031	(400) . (410)
25	108.86	2	27 16	0.2099	0.2076	($\bar{2}$32)
26	111.80	2	27 59	0.2202	0.2176	(080)
27	113.66	1	28 32	0.2282	0.2284	(242)
28	118.50	5	29 40	0.2450	0.2432	(421)
29	121.96	2	30 32	0.2581	0.2602	(431)
30	125.30	2	31 23	0.2712	0.2707	($\bar{3}$32)
31	128.00	1	32 4	0.2819	0.2825	(003)
32	130.90	2	32 47	0.2932	0.2945	($\bar{3}$42)
33	133.22	1	33 22	0.3025	0.2994	($\bar{2}$62)
34	135.42	2	33 55	0.3113	⎰ 0.3131 ⎱ 0.3154	(033) . (510)
35	143.04	1	35 49	0.3425	0.3412	($\bar{4}$22)
36	146.10	2	36 35	0.3552	0.3535	(432)
37	152.60	1	38 13	0.3827	⎱ 0.3846 ⎰ 0.3828	(243) . (303)
38	159.00	1	39 49	0.4100	0.4050	(063)
39	160.34	1	40 10	0.4160	0.4173	(480)
40	167.30	1	41 54	0 4460	0.4468	(343)
41	221.46	1	55 27	0.6783	0.6733	($\bar{3}$44)

$R = 57,2$ mM.; *Fe-α-* and *-β-radiation* ($\lambda_\alpha = 1,934$ Å). Exposition : 80 m. Amp. hours.
$a_o = 8,655$ Å ; $b_o = 16,58$ Å ; $c_o = 5,458$ Å ; $\beta = 89°32'$ (pseudo-rhombic).
Quadratic Formula; $\sin^2 \theta_\alpha = 0,01248 . h^2 + 0,0034 . k^2 + 0,03139 . l^2 -$
$$- 0,0003685 . hl.$$

§ 3. For the preparation of racemic *α-phenyl-1-aminopropane* we started from *propiophenone* (*ethyl-phenyl-cetone; propionylbenzene; α-oxo-α-phenylpropane* (boilingpoint: 218°—219° C.; meltingpoint: 21° C.). With free hydroxylamine in methylalcoholic solution this yields *ethyl-phenyl-cetoxime* (*propiophenone-oxime*): $CH_3 . CH_2 . C (: NOH) . C_6H_5$, which from its solution in ligroine can be obtained in beautiful tabular crystals of the meltingpoint: 54° C.

Its crystalform and structural properties are described in the following paragraph.

On reducing this compound by means of sodium + absolute alcohol in the way previously mentioned, the base finally was obtained in the form of a colourless liquid, which under a pressure of 3 m.M. boils at 62°—63° C. and which shows properties very analogous to those of the preceding base.

§ 4. *Crystalform and X-ray-Examination of Ethyl-phenyl-cetoxime*; meltingpoint: 54° C.

This oxime readily crystallizes from a solution in ligroine in the shape of thick prismatic crystals (*A*), or from methyl- or ethylalcohol in hexagonally-bounded plates (*B*) (Fig. 2). The substance is very soluble, but it easily crystallizes in well developed individuals.
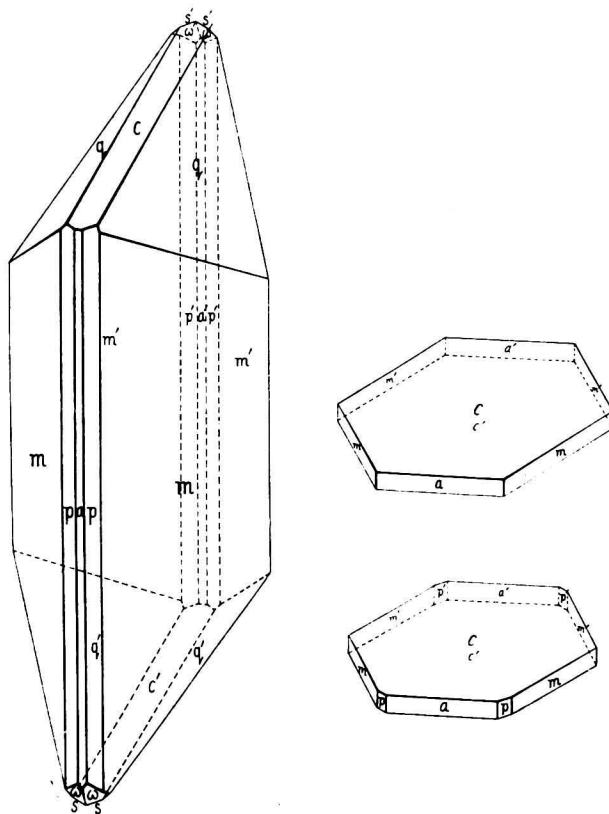
A. Crystals from ligroine.   *B.* Crystals from methyl- or ethyl-alcohol.
Fig. 2. Crystalform of Propiophenone-oxime. (54° C.).

They are *monolinic-prismatic,* with the axial ratio:

$$a : b : c = 1,6981 : 1 : 1,2056;$$

$$\beta = 69°20'.$$

Forms observed: $m = \{110\}$, broad and lustrous; $p = \{210\}$ equally lustrous, but narrower than m; $a = \{100\}$, mostly rather narrow, sometimes equally broad as m, yielding bright reflexions; $c = \{001\}$, often narrower than q, but in the case of the tabular crystals predominant and giving sharp images; $q = \{011\}$, broad, well reflecting; $\omega = \{211\}$ and $s = \{112\}$, both only small and subordinate and yielding only dull images.

Angular values:			Observed:	Calculated:
$m : c$	$= (110) : (001) =$	*79°14′		—
$m : m$	$= (110) : (1\overline{1}0) =$	*64 20		—
$m : q$	$= (110) : (011) =$	*59 26		—
$m : q$	$= (110) : (0\overline{1}1) =$	40 41		40°42′
$c : q$	$= (001) : (011) =$	48 28		48 26½
$a : c$	$= (100) : (001) =$	69 15		69 20
$m : p$	$= (110) : (210) =$	19 20		19 21
$p : a$	$= (210) : (100) =$	38 34		38 29
$p : \omega$	$= (\overline{2}10) : (\overline{2}11) =$	32 30		31 58
$a : m$	$= (100) : (1\overline{1}0) =$	57 50		57 50
$c : s$	$= (001) : (\overline{1}12) =$	37 25		36 47
$s : m$	$= (\overline{1}12) : (\overline{1}10) =$	63 31		64 0

The plane of the optical axes, is according to Dr. TERPSTRA, perpendicular to $\{010\}$; the first bissectrix lies in $\{010\}$, the second is parallel to the b-axis, which is the optical normal.

The cleavability is parallel to $\{100\}$.

The density of the crystals at 15° C. was found to be: 1,192. The crystals are pseudo-rhombic: on turning them round the c-axis through 180° and attributing to the different forms the symbols: $c = \{102\}$, $a = \{\overline{1}00\}$, $q = \{112\}$, $s = \{011\}$ and $\omega = \{212\}$, the parameters become: $a' : b' : c' = 1,5883 : 1 : 1,2056$ with $\beta' = 89°52\frac{1}{2}'$.

From rotation-spectrograms (*Fe*-radiations, $\lambda_\alpha = 1,934$ Å) round the a-, b- and c-axis, the dimensions of the elementary cell were found to be: $a_0 = 12,72$ Å; $b_0 = 7,68$ Å and $c_0 = 9,03$ Å; so that the cell contains a mass equal to *4* molecules.

A powder-spectrogram yielded the following data (Table II):

§ 5. For the preparation of *β-phenyl-α-propylenediamine* we equally started from *propiophenone,* which by means of methyl-alcohol and N_2O_3 was first transformed [4]) into *α-isonitroso-propiophenone* (*methyl-benzoyl-*

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[4]) Conf.: *Organic Syntheses,* XVI, 44.

No of Line:	2 l in mM.	Intens: (estin)	Rad λ:	θ:	sin² θ: (observed)	sin² θ: (calculated)	Indices:
				TABLE II. Powder-Spectrogram of Propiophenone-oxime; meltingpoint: 54° C.			
1	25.46	2	α	6° 22½'	0.0123	0.0131	(001); (101)
2	27.96	2	α	7 0	0.0148	0.0158	(010)
3	38.90	3	α	9 44½	0.0286	0.0289	(011); (111)
4	42.68	4	β	10 41½	0.0344	0.0378	($\bar{1}$11)
5	47.12	8	α	11 48	0.0418	0.0421	($\bar{1}$11)
6	51.80	4	α	12 58½	0.0504	0.0524	(002); (202)
7	54.16	1	β	13 34	0.0550	0.0535	(300)
8	56.54	2	α	14 9½	0.0598	0.0594	(300)
9	59.46	3	β (α)	14 53½	0.0660	$\begin{cases} \alpha = 0.0682 \\ \beta = 0.0652 \end{cases}$	α (012); β (302)
10	62.34	6	α	15 37	0.0724	0.0724	(302)
11	64.60	1	α	16 11	0.0776	0.0765	(021); (121)
12	68.06	2	α	17 3	0.0859	0.0879	($\bar{1}$12)
13	70.08	5	α	17 33	0.0909	0.0922 to 0.0925	($\bar{3}$01); (401)
14	74.24	1	β	18 35½	0.1017	0.1060	(003)
15	80.12	5	α	20 4	0.1177	0.1179	(003)
16	82.00	1	α	20 32	0.1230	0.1207 to 0.1228	(113); (320)
17	86.00	2	α	21 32½	0.1348	0.1337; 0.1341 to 0.1358	(013); (313); (322)
18	88.80	1	α	22 14	0.1432	0.1427 to 0.1442	(030); ($\bar{1}$03)
19	93.70	4	α	23 28	0.1586	0.1600	($\bar{1}$13)
20	96.24	1	α	24 6	0.1667	0.1670	($\bar{3}$12)
21	100.20	2	β (α)	25 3	0.1792	0.1756 to 0.1760	(032); ($\bar{2}$31); (331); α: (510)
22	104.82	4	α	26 15	0.1956	0.1951 to 0.1955	(032); ($\bar{2}$31); (232) (331)
23	107.42	1	α	26 54	0.2047	0.2058	(114)
24	109.84	2	α	27 31	0.2134	0.2146	($\bar{3}$22)
25	111.80	2	β	28 0	0.2204	0.2228 to 0.2235	($\bar{4}$32); ($\bar{4}$30); ($\bar{2}$32); (331); (233)
26	116.82	1	α	29 15½	0.2389	0.2364 to 0.2376	($\bar{3}$03); (600)
27	119.40	3	α	29 54	0.2485	0.2476 to 0.2483	($\bar{4}$32); ($\bar{4}$30); ($\bar{2}$32); (133); (233)
28	124.80	2	α	31 15	0.2691	0.2668	(041); (141)
29	127.50	1	α	31 55½	0.2796	0.2799	($\bar{1}$41)
30	129.12	2	α	32 20	0.2861	0.2869; 0.2874	($\bar{1}$33); (433)
31	130.63	2	α	32 43	0.2921	0.2939	($\bar{3}$32)
32	134.00	1	α	33 33½	0.3055	0.3061 to 0.3045	(042); ($\bar{1}$24); ($\bar{2}$14)
33	135.60	1	β	33 57½	0.3120	0.3122	($\bar{3}$04); (441)
34	140.40	2	α	35 9½	0.3315	0.3329	(334)
35	144.10	4	α	36 5	0.3469	0.3478 to 0.3461	($\bar{3}$04); (441)
36	146.10	1	α	36 35	0.3552	0.3520 to 0.3586	($\bar{2}$24); (434); ($\bar{2}$42); ($\bar{4}$32); (243) or (034)
37	151.70	2	α	37 59½	0.3620	0.3657	($\bar{4}$23)
38	153.50	1	α	38 26½	0.3865	0.3829	($\bar{1}$15)
39	157.90	1	α	39 32½	0.4053	0.4049	($\bar{3}$42)
40	162.10	3	α	40 35½	0.4234	0.4202	($\bar{4}$04)

$R = 57{,}2$ mM. Radiation: Fe $\alpha(\beta)$; $\lambda_\alpha = 1{,}934$ Å. Exposition: 60 m.A.h.

Monoclinic-prismatic: $a_o = 12{,}72$ Å; $b_o = 7{,}68$ Å; $c_o = 9{,}03$ Å; $\beta = 69° 20'$

Quadratic formula: $\sin^2 \theta_\alpha = 0{,}0066017 \cdot h^2 + 0{,}015854 \cdot k^2 + 0{,}01310 \cdot l^2 - 0{,}0065641 \cdot hl$.

The elementary cell contains the mass of 4 molecules; the density of the crystals $= 1{,}192$ at 0° C. (calculated).

cetoxime): $C_6H_5 . CO . C(:NOH) . CH_3$, melting at 114° C. The crystallographical and structural properties of this compound are described in § 6.

By repeated treatment [5]) of this substance with free hydroxylamine in methyl-alcoholic solution, the corresponding *methyl-phenyl-glyoxime* (*acetyl-benzoyldioxime*; *a-β-dioximino-a-phenylpropane*):

$$C_6H_5 . C(:NOH) . C(:NOH) . CH_3$$
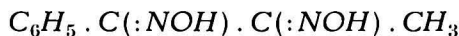
was obtained, which in the pure state proved to melt at 238°—240° C. This sparely soluble compound readily crystallizes from a number of solvents, but always in the form of spherolithically-aggregated, very small, opaque crystals. So great is its tendency towards aggregation, that we found it quite impossible to obtain the substance in free, isolated individuals.

For this reason, no crystallographical or roentgenographical analysis has been made.

As a reduction of this glyoxime in acid solution, — e.g. with tin and hydrochloric acid (KOLB; GABRIEL), — yields *2-5-dimethyl-3-6-diphenyl-pyrazine*, we tried the reduction by means of sodium + absolute alcohol in excess (see in the above); indeed, the yield of the base desired now proved to be almost the theoretical one.

The *1-Phenyl-1-2-diaminopropane* (*β-phenyl-a-propylenediamine*) thus obtained is a colourless, strongly refracting liquid, which under a pressure of 2 to 3 m.M. boils at 93° C. Even in the darkness, the base shows a tendency towards assuming a pale yellow colour.

Its specific weight at 18° C. proved to be: *1,0131*. The liquid has a bitter and burning taste, but less intensive than that of the two monovalent bases already described.

Even in a bath of solid CO_2 and alcohol the racemic base does *not* crystallize: it changes into a very viscous liquid, finally into a glassy mass, in which no trace of crystals appear.

The chloride and the nitrate are very soluble in water, the sulphate much less so. On adding strong hydrochloric or nitric acid to the yellowish base dissolved in water, the solution turns violet; this colour is, however, changed into a yellow one on boiling the aqueous solution for a short time.

Finally the sulphate was obtained from its aqueous solution in a perfectly colourless aggregation of small, thin plates.

§ 6. *Crystalform and X-ray-study of Isonitroso-propiophenone* (*methyl-benzoylcetoxime*); meltingpoint: 114° C.

This substance crystallizes from acetone, ethyl-alcohol and, preferentially, from methylalcohol in lustrous, transparent tables Fig. 3 (*A*); from chloroform or chloroform + ligroïne in more or less elongated prisms (*B*) with often rather irregularly developed terminal forms.

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[5]) The process (10 % excess of hydroxylamine) must at least twice be repeated, because the reaction-velocity is rather small and the first time, therefore, the transformation often proves to be still incomplete, yielding a mixture of the mono- and dioximes.

The crystals are *monoclinic prismatic*, with the parameters:
$$a : b : c = 0,6894 : 1 : 0,4397;$$
$$\beta = 73°6'.$$

Forms observed: $a = \{100\}$ predominant, often with a fine vertical striation; in the latter case the reflexions are dull, otherwise they are very lustrous; $m = \{110\}$ and $b = \{010\}$, well developed and yielding sharp
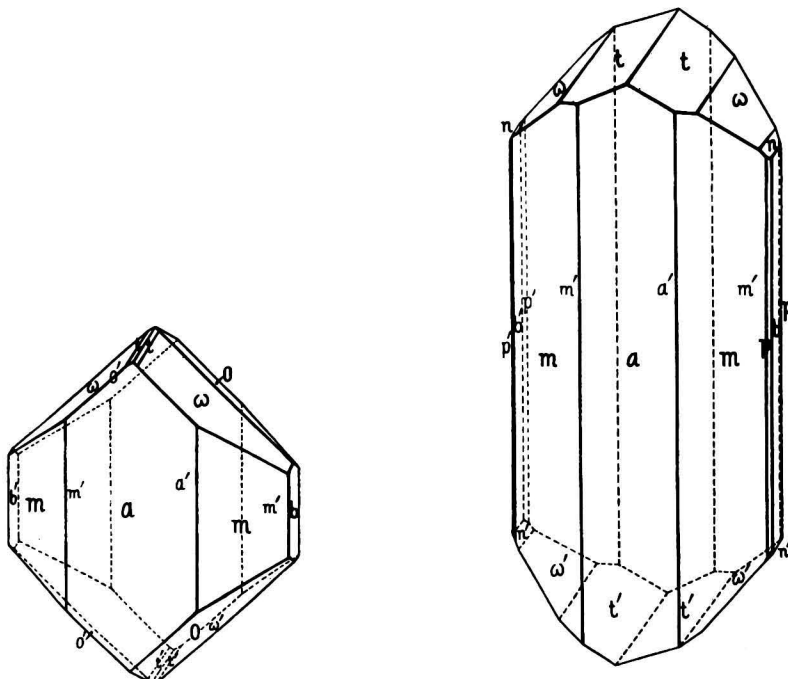
A. Crystals from methylalcohol or acetone.   B. Crystals from chloroform or ligroine.
Fig. 3. Crystal form of Isonitroso-propiophenone (114° C.).

images; $o = \{121\}$ and $\omega = \{021\}$, about equally broad and giving bright reflexions; $t = \{011\}$, narrow, sometimes broader; $n = \{031\}$, small, sometimes absent, — but when present, well reflecting; $p = \{120\}$, much narrower than m, but yielding good images.

Furthermore: $l = \{210\}$ and $k = \{410\}$, both extremely narrow and scarcely visible; these forms yield dull reflexions or are often absent. With the prismatic crystals (B), the faces a and m often show a fine vertical striation, which is absent with the crystals (A) deposited from alcohol.

The crystals are perfectly cleavable parallel to $\{010\}$.

Angular Values:	*Observed:*	*Calculated:*
$a : m = (100) : (110) =$	$\star 33°24\frac{2}{3}'$	—
$o : o = (\bar{1}21) : (1\bar{2}1) =$	$\star 79\ 28$	—
$a : o = (\bar{1}00) : (\bar{1}21) =$	$\star 74\ 46\frac{1}{2}$	—
$b : m = (010) : (110) =$	$56\ 35\frac{1}{3}$	$56°35\frac{1}{3}'$
$b : p = (010) : (120) =$	$37\ 10$	$37\ 10$

$p : m =$	$(120) : (110) =$		19	29	19	$25\frac{1}{3}$
$a : k =$	$(100) : (410) =$ ca.	9	40		9	22
$k : l =$	$(410) : (210) =$ ca.	8	50		8	$53\frac{1}{3}$
$l : m =$	$(210) : (110) =$ ca.	15	10		15	$9\frac{1}{2}$
$\omega : a =$	$(021) : (100) =$		77	13	77	9
$\omega : \omega =$	$(021) : (0\bar{2}1) =$		80	12	80	9
$b : \omega =$	$(010) : (021) =$		49	54	49	$55\frac{1}{2}$
$o : \omega =$	$(\bar{1}21) : (021) =$		28	2	28	$4\frac{1}{2}$
$b : o =$	$(010) : (121) =$		50	17	50	18
$\omega : t =$	$(021) : (011) =$		17	6	17	$15\frac{1}{2}$
$t : t =$	$(011) : (0\bar{1}1) =$		45	47	45	38
$b : n =$	$(010) : (031) =$		38	25	38	$23\frac{1}{2}$
$n : \omega =$	$(031) : (021) =$		11	31	11	32

On {100} a rectangular, on {110} a slightly, on {010} a clearly inclined extinction proves to be present.

The plane of the optical axes is, according to Dr. TERPSTRA, perpendicular to {010}; the b-axis is the first bissectrix; the dispersion is "crossed" and on {010} the exit of the two axes is observable.

The specific weight was found to be 1,288 at 16° C.

From rotation-spectrograms (iron-a-radiation) round the c-axis (sin $\mu = 0,247$), c_0 was found to be 6,23 Å; from a SAUTER-diagram, b_0 proved to be 14,3 Å ($d_{100} = 9,36$ Å).

From a rotation-spectrogram round the zône-axis: b-ω-t-t; the value of sin μ was found to be 0,1591; so that $a_0 = 9,68$ Å. As $\beta = 73°6'$, it follows that the elementary cell contains a mass of 4 times the molecular weight; the calculated density at 0° C. in that case is: $d_0 = 1,304$.

The SAUTER-spectrogram round the c-axis yielded the most intensive spots for the following indices-triplets (arranged in sequence of decreasing intensities: (040), (110), (200), (210), (150), (230); (130), (240), (440), (250), (330), (350); (220), (510), (160), (170), (300); and several of smaller intensities, like: (060), (260), (410), (310), (320), (340), (370), (470), (550), (570), (620), (660), (740), etc. Several of these have also been met with in the powder-spectrogram recorded in Table III (on the following page).

§ 7. Resolution of Benzedrine into its Optical Antipodes.

Racemic *benzedrine*: $C_6H_5 . CH_2 . CH(NH_2) . CH_3$ was resolved into its optical antipodes by repeated fractional crystallization of the *bi-tartrates* from 92 % alcohol. The *bi-d-tartrate* was nine times recrystallized from the *boiling* solvent; after cooling to roomtemperature, the salt is deposited in the form of small colourless crystals melting, when pure, at 183° C. In general, the resolution evidently takes place in the way described by LEITHE [6]). The final solutions containing the salt of the levogyratory

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⁶) W. LEITHE, Ber. d.d. chem. Ges., **65**, 660 (1932).

TABLE III.

Powder-Spectrogram of Isonitroso-propiophenone; meltingpoint: 114° C.

No of Line:	$2l$ in mM.	Intens: (estim.)	Rad λ:	θ:	$\sin^2 \theta$: (observed)	$\sin^2 \theta$: (calculated)	Indices:
1	23.44	3	α	5°52½′	0.0105	0.0109	(100)
2	25.84	3	β	6 28	0.0127	0.0138	(110
3	28.46	3	α	7 7⅞	0.0154	0.0155	(110)
4	30.80	2	α	7 43	0.0180	0.0183	(020)
5	41.26	1	α	10 20	0.0322	0.0319	(111)
6	44.22	2	α (β)	11 42⅛	0.0412	0.0411	(030); β (200)
7	49.00	8	α	12 16⅛	0.0452	0.0436; 0.0456	(200); (121)
8	53.66	3	α	13 26	0.0540	0.0520; 0.0548	(130); (211)
9	55.22	2	β	13 49½	0.0571	0.0558	(220)
10	57.40	4	α	14 22½	0.0616	0.0619	(220)
11	61.00	8	α	15 16½	0.0694	0.0685; 0.0676	(131); (221) or (031)
12	63.36	8	α	15 52	0.0747	0.0732	(040)
13	67.50	3	α	16 54½	0.0846	0.0847; 0.0841	(230); (140)
14	69.20	3	α	17 19½	0.0887	0.0882	($\bar{1}$31)
15	74.02	6	α	18 32	0.1010	0.1010; 0.1005	(112); (141)
16	77.84	2	α	19 29	0.1112	0.1132	(321)
17	81.34	4	α	20 22	0.1211	0.1202	($\bar{1}$41)
18	83.02	2	α	20 47½	0.1260	0.1252; 0.1278	(150); (222)
19	86.04	2	α	21 32½	0.1348	0.1392; 0.1358	(330); ($\bar{1}$02)
20	93.40	1	α	23 23½	0.1576	0.1579; 0.1585	(250); ($\bar{3}$11)
21	95.80	1	α	23 59½	0.1653	0.1646; 0.1659	(060); (411)
22	113.72	1	α	28 28½	0.2273	0.2271; 0.2294	($\bar{3}$41); ($\bar{2}$32) or ($\bar{3}$41)
23	121.54	2	α	30 26	0.2566	0.2584; 0.2551	($\bar{4}$21); (023)
24	126.24	1	α	31 37	0.2748	0.2725; 0.2773	(500); ($\bar{1}$03)

Radius of The Camera: 57,2 mM. *Fe-α* and *-β*-radiation: $\lambda_\alpha = 1,934$ Å. Exposure: 100 m.A.h. Quadratic formula: $\sin^2 \theta_\alpha = 0,0109 . h^2 + 0,004573 . k^2 + 0,02632 . l^2 - 0,009847 . h.l.$ Monoclinic-prismatic; $a_o = 9,68$ Å; $b_o = 14.3$ Å: $c_o = 6,23$ Å; $\beta = 73°6'$. $Z = 4$ mol. in the elementary cell.

base, then were treated with *KOH* and the free base thus obtained transformed into the *bi-l-tartrate* by means of *l-tartaric acid*: after four recrystallizations this bitartrate did not change its specific rotation anymore.

The *bitartrates* are anhydrous; they crystallize in small, lustrous prisms or in flat plates of rectangular shape. They belong to the *monoclinic-sphenoidal* class, with the axial ratio:

$a : b : c = 1,7604 : 1 : 1,1841$; $\beta = 87°52'$ and they are evidently of a pseudo-rhombic type. (Fig. 4). The crystals of *d-benzedrine-bi-d-tartrate* are enantiomorphous to those of *l-benzedrine-bi-l-tartrate*. They show the

forms: $a = \{100\}$, very lustrous; $m = \{110\}$, and $p = \{110\}$, well developed, moderately well reflecting, but duller than a; $c = \{001\}$, sometimes broader, sometimes narrower, always yielding good reflections, — just like $r = \{\bar{1}01\}$, which, however, is mostly narrower than c and yields reflections of a variable lustre; $\omega = \{111\}$ *bi-tartrate* with the *levogyrate*, ($o = \{111\}$ is, however, often absent with the *dextrogyrate bitartrate*) is always small, but well measurable; $s = \{201\}$, very narrow in the case of the levogyrate, but broader with the dextrogyrate crystals, yields feeble reflections, as Dr. TERPSTRA more particularly stated. The angular values of the different individuals oscillate within rather wide limits. Twins round the c-axis.
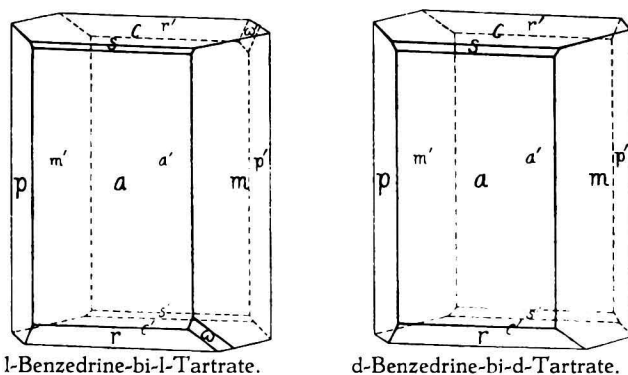

l-Benzedrine-bi-l-Tartrate.   d-Benzedrine-bi-d-Tartrate.

Fig. 4.

Angular values:	Observed:	Calculated:
$a : m = (100) : (110) =$	*60°23′	—
$c : r = (001) : (\bar{1}01) =$	*34 35	—
$a : c = (100) : (001) =$	*87 52	—
$a : p = (100) : (1\bar{1}0) =$	60 20	60°23′
$c : \omega = (001) : (111) =$	54 4	54 23
$\omega : a = (\bar{1}11) : (\bar{1}00) =$	68 5	67 43
$\omega : p = (\bar{1}11) : (1\bar{1}0) =$	37 0	36 41
$a : s = (100) : (201) =$	35 48	35 $51\frac{1}{2}$
$c : s = (001) : (201) =$	52 4	52 $0\frac{1}{2}$

The crystals are perfectly cleavable parallel to $\{100\}$.

The axial plane is $\{010\}$; on $\{100\}$ generally the exit of one axis (and by twin-formation, occasionally that of two disturbed axes) is observable. Strong, *inclined* dispersion, with $\varrho < v$ round the first bissectrix of positive character, which is oblique to $\{100\}$. The axial image occasionally appears to be somewhat disturbed as a consequence of the twin-formation round the c-axis. The density of the crystals was 2,169 at 17° C.

From rotation-diagrams obtained by means of *Fe* -radiation round the a-, b-, c-axis (and round [110], $I = 14,64$ Å by Dr. TERPSTRA), the dimensions of the elementary cell were found to be: $a_0 = 12,76$ Å; $b_0 = 7,17$ Å; $c_0 = 8,41$ Å. The elementary cell, therefore, evidently contains

a mass of *4* molecules. The density was calculated at *2,186* at 0° C.; and $a_0 : b_0 : c_0 = 1,7796 : 1 : 1,1729$.

The rotatory dispersion of these salts was measured; the results are collected in Table IV.

	Specific Rotations [α] of		Mean Values of the Dispersion:
Wave-length in A.U:	*d*-Benzedrine-bi-*d*-tartrate:	*l*-Benzedrine-bi-*l*-tartrate:	
6730	—	−25°.6	25°.4
6480	+26°.5	−27.0	26.7
6262	+27.3	−28.5	27.9
6074	+29.5	−30.5	30.0
5893	+31.8	−32.0	31.9
5735	+33.4	−33.5	33.4
5592	+35.4	−36.4	35.9
5463	+37.5	−39.4	38.4
5340	+39.0	−40.9	39.9
5225	+41.8	−42.3	42.1
5126	+44.0	−44.3	44 1
5036	+45.5	−46.3	45.9
4950	+47.1	−47.8	47.4
4861	+49.8	−50.7	50.2
4793	+54.0	−53.7	53.8

TABLE IV. Retatory Dispersion of the Bi-tartrates.

The measurements were made in 2⁰/₀ aqueous solutions of the salts.

From these *bi-tartrates* the optically-active bases were set free, thoroughly dried and distilled in a high vacuum: the *d-benzedrine* boiled at 60° C. under 4 m.M., at 68° C. under 7 m.M. pressure, at 70° C. under 8 m.M. and at 80° C. under 12 m.M. pressure. The pure *l-benzedrine* boiled at 76° C. under a pressure of 10 m.M., at 80° C. under 12 m.M. and at 85° C. under 15 m.M. pressure.

The pure optically-active benzedrines are colourless, strongly refracting liquids, with a density of *0,9342* at 18° C.: for the *d*-base the value obtained was 0,9337, for the *l*-base 0,9346. Their taste is very bitter and strongly burning and not appreciably different either from each other, or from that of the racemic compound.

The refractive index of the antipodes for *Na*-light is *1,545*. They do not crystallize in a bath of ice and sodium chloride, but readily do so in a bath of solid CO_2 and alcohol in which they are transformed into an aggregation of plate-shaped, colourless crystals. The rate of crystallization is, however, very small; once solidified, the crystals, on cautiously heating them very slowly, are transformed into a soft mass, without it being possible to fix a *sharp* meltingpoint of the solid substance. Endeavours to do this gave a maximum separation of the temperature-time-curves for the heating-bath and the air-surrounded solid substance, at about + 27°,5 C., although the

gradual softening of the mass already sets in at about 19° C. The solid substance is rather volatile and the molten mass yields a sublimate already as low as 40° C.

Wave-length in A.U.:	Specific Rotations [α] of		Mean Values of the Dispersion:
	d-Benzedrine:	*l*-Benzedrine:	
7280	$+23.40$	-22.62	23.0
6980	$+24.03$	-23.79	23.9
6730	$+26.15$	-25.88	26.1
6480	$+28.59$	-28.32	28.4
6262	$+31.07$	-30.82	30.9
6074	$+33.50$	-33.30	33.4
5893	$+35.97$	-35.72	35.8
5735	$+38.53$	-38.13	38.3
5592	$+41.05$	-40.64	40.8
5463	$+43.56$	-43.10	43.3
5340	$+46.15$	-45.59	45.9
5224	$+48.74$	-48.15	48.4
5126	$+51.31$	-50.59	50.9
5036	$+53.87$	-53.10	53.5
4950	$+56.47$	-55.61	56.1
4861	$+58.91$	-58.04	58.5
4793	$+61.67$	-60.58	61.1
4724	$+64.19$	-62.99	63.6
4658	$+66.98$	-65.21	66.1
4596	$+69.80$	-67.52	68.9
4537	$+72.05$	-70.46	71.3
4483	$+74.81$	-73.45	74.1
4430	$+76.36$	—	76.3
4380	$+80.47$	—	80.4

TABLE V.   Rotatory Dispersion of *d*- and *l*-Benzedrine.

The salts of *benzedrine*, as well of the racemic as of the optically-active bases, all crystallize badly: the solutions have a strong tendency to super-saturation and the salts are usually deposited as conglomerations of fine needles. The sulphate still crystallizes the best: the sulphates of the optically-active bases are deposited as aggregations of extremely thin, rectangularly shaped plates which contain water of crystallization, but loose it most rapidly in contact with the air. The thin lamellae of the sulphate show, between crossed nicols, a rectangular extinction; in con-vergent light the plates prove to be perpendicular to the second bissectrix. The crystals are most probably ortho-rhombic. The rotary dispersion of the anhydrous sulphates is represented in Table VI.

These data — including those for the antipodes of *a-phenylpropyl-*

amine which will be communicated in a following paper, — are graphically represented in Fig. 5.
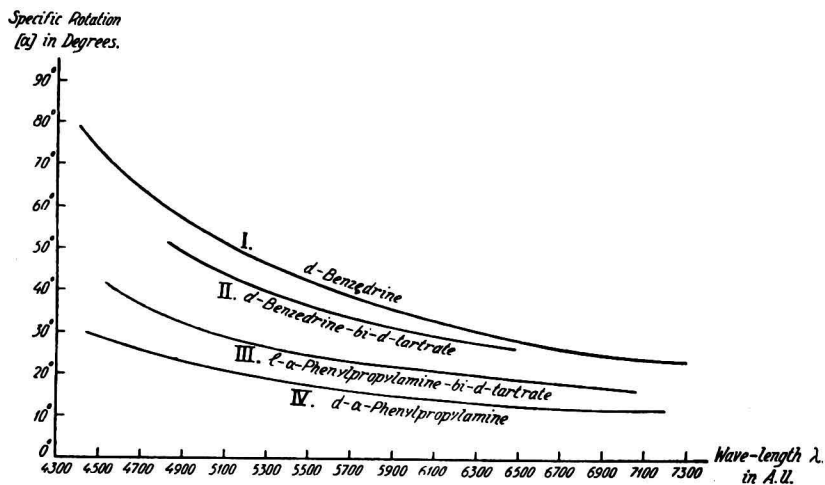

Fig. 5. Rotatory Dispersion of the Bitartrates and of the free Bases.

TABLE VI.	Rotatory Dispersion of *d*- and *l*-Benzedrine-Sulphate.		
Wave-length λ in A.U.	Specific Rotation [a]	Specific Rotation [a]	Mean Rotation [a]
6980	+15°.5	—18°.0	±16°.7
6730	+18.5	—20.0	19.3
6480	+20.3	—	20.3
6262	+21.5	—23.5	22.5
6074	+23.3	—25.1	24.2
5893	+24.3	—26.2	25.3
5735	+27.0	—27.5	27.2
5592	+29.2	—	29.2
5463	+31.0	—29.5	30.3
5340	+33.0	—	33.0
5224	+34.5	—33.2	33.9
5126	+36.2	—	—
4950	—	—36.3	36.3
4793	+40.0	—37.4	38.7
4658	+42.3	—	42.3
4596	—	—46.0	46.0
4483	+46.5	—48.2	47.4
Measured in Solutions of 2%.			

Evidently the rotatory dispersion of the optically-active *benzedrines* themselves and of their *salts* is in algebraic sign quite *analogous*; as later-on will be demonstrated, this is *not* longer true in the case of its isomeride.

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