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# ABSOLUTE CONFIGURATION OF THE ALKALOID (+)SEDRIDINE AND OF (−)ALLOSEDRIDINE

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**Abstract**—Details of the correlation of configuration[1,2] of natural, (+)sedridine at the OH-bearing carbon with *S*(+) 2-octanol, **4** → **5** → **6**, and some alternate attempts are described. The von Braun amide degradation reaction which has been explored only once before for a similar purpose, led to the conclusion, when applied to **4**, that (+)sedridine has the 2*S*. 2′*S* absolute configuration, **8**.

(−)Allosedridine, **10**, the C-2′ epimer of (+)sedridine was then converted into the *p*-nitrophenylpiperidooxazine and both the relative and the absolute configuration of the latter were determined by X-ray diffraction as *R* at the carbinol carbon and *S* at the other centers, **9**. The configurational assignments are in full agreement with those based on an ORD-CD study[3,4] of (+)allosedridine and (−)sedridine. [Sedridine; allosedridine; alkaloids; configuration; correlation; X-ray; anomalous scattering; NMR; spin-decoupling: von Braun reaction; *S*(+)2-octanol].

IN PRELIMINARY reports[1,2] two of us have described elucidation of the absolute configuration of the piperidine alkaloid (+)sedridine. We now wish to describe in full this experimental work, also some of our alternative approaches and the completion of these with the recent determination by X-ray diffraction of the absolute configuration of (−)allosedridine.

Sedridine has been isolated from *Sedum acre* by Beyerman's[6] and Schöpf's[7] groups independently, also described by Franck,[8] and the constitution of a 2-piperidyl-2-propanol[9] was ascribed.[6] Synthesis of the two racemates by catalytic hydrogenation of (±)2-picolylmethylcarbinol (further quoted as PMC) in acidic medium was described.[10] Separation *via* picrates and resolution of the base (from the more soluble picrate) with N-acetyl L-leucine then gave (+)sedridine (10% yield). Some improvement of this technique was claimed[10] by oxidizing the racemic mixture to (±)pelletierine and reducing the latter to (±)sedridine. A more selective approach[11] to sedridine made use of stepwise separation of isomers: resolving (±)PMC first with (−) or (+)dibenzoyltartaric acid and then submitting (+) and (−)PMC separately, with no added acid, to catalytic hydrogenation. Purification by vacuum sublimation, or alternately recrystallization of the salt of (+) derivative with L-acetylleucine then led to optically pure (+)sedridine. Recently a further four-step synthesis of sedridines *via* N-benzyl 1,2-piperideine was described by Schöpf, *et. al.*[12] Resolution of (±) allosedridine has finally been achieved[4] by using 6,6′-dinitro-2,2′-diphenic acid.

Configurational assignments were made first by oxidation of (−)sedridine to *R*-pipecolic acid.[13] Previously, (+)conhydrine gave[14] on oxidation (−)pipecolic acid, the absolute configuration of which was already determined[15] as being *S*. Therefore, *S* configuration at C-2 in both (+)sedridine and (+)conhydrine was ascertained. A study aiming at determination of the relative configuration of (±)sedridine and (±)allosedridine was based on comparison by NMR of the *p*-nitrophenyloxazines.[16] Since the amount

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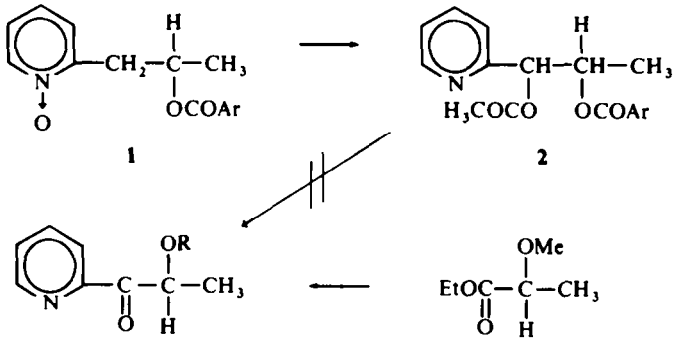
of oxazines obtained on purification was less than quantitative, *cis* and *trans* oxaquinolizidines could equally be formed from both racemates, and thus configurational conclusions on a conformational basis seemed[17] somewhat ambiguous. However, quite recently[18] it was concluded that in 1,3-heteroatomic systems like piperidooxazines a *cis*-fused system is less probable although the unfavorable dipolar 'interaction" i.e., anomeric effect[19,20] or "rabbit ear effect".[21] Edward–Lemieux effect.[22] was relieved. Namely, this gain is overcompensated[18] by introducing two *gauche*-butane and one *gauche*-propanol interaction into the molecule.

At this stage we became involved in the configurational problem of ε-coniceines of Löffler,[23,9] hence, in the determination of the propanol carbon in sedridine. This seemed fascinating from the point of view of biosynthesis, too, for (i) natural conhydrine and sedridine have closely related constitutions.[6,9] (ii) they have the same configuration at the piperidine C-2 atom,[13,14] and (iii) (+)PMC and (+)2-pyridylethyl carbinol have shown the same steric selectivity in catalytic hydrogenation leading preferentially to (+)sedridine[11] and (+)conhydrine,[24] respectively.



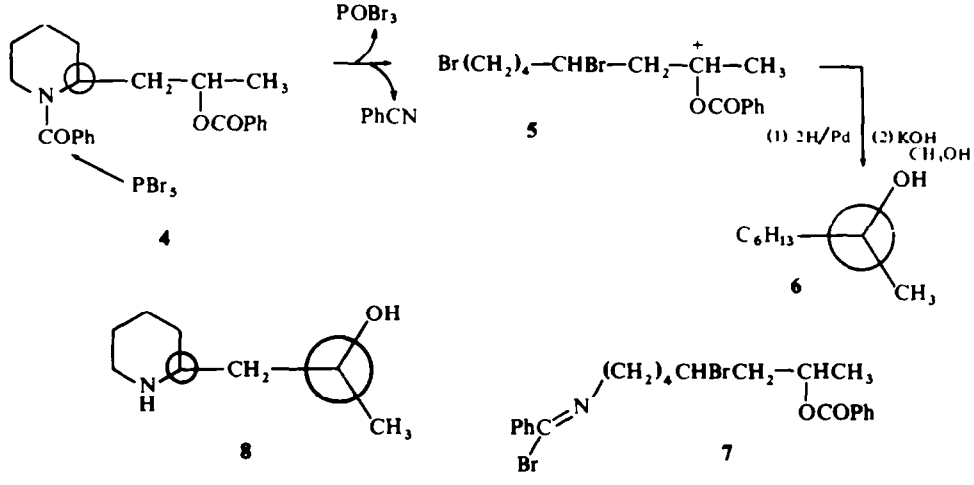

We first attempted correlation of L(+) lactic acid with (+) or (−)PMC.* thus with (+) or (−)sedridine.[2b] To this end optically active *p*-nitrobenzoyl PMC was oxidized to the amineoxide **1** $[\alpha]_D$ 178°, the latter subjected to Polonovski rearrangement by acetic anhydride and the mixture of (−)epimers of 1-acetoxy 2-*p*-nitrobenzoyloxy 2-pyridyl 1,2-propanediol **2**, we isolated in optically active form. "Second" Polonovski reaction, on the amineoxide of **2** failed, as has happened in other cases,[26] however, to give the ketone **3**, *R* = *p*-nitrobenzoyl. The methyl ether **3**, R = $CH_3$ was obtained[27] in optically pure form from 2-picolyl lithium and D (−) lactic acid methyl ether methyl ester for comparison. Deoxygenation of 2-(D-methoxypropionyl)pyridine to (+) or (−) PMC methyl ether was accompanied by complete racemization, therefore this line was abandoned. Decker oxidation similar to that of nicotine,[28] of (−) O-*p*-nitrobenzoyl PMC methiodide resulted in demethylation,[2b] rather than in formation of an α-pyridone that probably could have been degraded to L or D-2-hydroxybutyric acid.

Owing to these partly futile efforts our attention turned towards application of the von Braun amide degradation reaction.[29] This has previously been adopted once by Prelog and Zalan[30] to correlate the quinuclidine moiety of quinine with 3-ethyl-4-

* Optical purity of PMC was checked by NMR through diastereotopic signals

methylnonane. Now (+)sedridine was benzoylated and (−)O,N-dibenzoyl sedridine **4** with phosphorus pentabromide heated to 80° giving 60% phosphorus oxybromide but no benzonitrile. Distilling the residue under $10^{-3}$ mm pressure at 110–120° then gave first benzonitrile, and next 50% *dextrorotatory* 4,8-dibromo-2-octylbenzoate, **5**. The 60 Mc NMR spectrum showed as expected 5 aromatic protons at $\delta$ 7·5, and two strongly deshielded methine protons at $\delta$ 5·60(t) and 5·18(q), $\underline{H}_2C$—Br at $\delta$ 3·33, an envelope of 8H between 2·9–1·53 ppm, and (C—$C\underline{H}_3$) at 1·33(t). Irradiating the latter at 231 c/s causes the quartet at $\delta$ 5·18 to collapse and *not* the lower field methine proton. Thus the $\underline{H}$—C—Br seemed, unexpectedly, to be more deshielded than $\underline{H}$—C—O at C-2′.

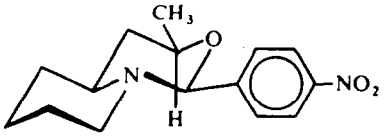
Changing the technique of elaboration, i.e., stopping distillation of the reaction mixture after removal of benzonitrile and separating the residue by TLC, gave a dibromooctyl benzoate with comparable analytical figures and $[\alpha]_D$ value, however, of somewhat different NMR spectrum as to the methine protons: $\delta$ 5·45(m) and 4·23(m). Fig 1 gives details of this curve, also of double irradiation. This operation proved (a) that C—$CH_3$ $\delta$ 1·45(d) is coupled with a proton at 240·5 c/s downfield at 5·45 ppm; (b) $\underline{H}$—Br resonating at $\delta$ 4·23 is coupled with a multiplet at 155 c/s upfield, probably on H-5; (c) the terminal $\underline{H}_2C$—Br is coupled with a part of the envelop centered at 82 c/s upfield.



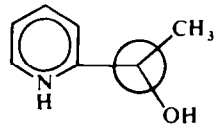

The discrepancy between the dibromo esters disappeared, however, on catalytic hydrogenolysis over Pd–C in methanol, both affording (+)2-octylbenzoate that was subsequently hydrolized to *S*(+)2-octanol,[31] **6**, $[\alpha]_D$ +8·78°. The two specimina of **5** we isolated could be diastereoisomers at the secondary carbon no. 5 with methine protons, differently shielded by the adjacent phenyl group. Alternately, one could not preclude that the product which was isolated by distillation underwent carbonium ion rearrangement, e.g., into 3,8-dibromo 2-octylbenzoate. However, the product from TLC did not rearrange during distillation. Treatment of (−)O,N-dibenzoyl allosedridine with phosphorus pentabromide gave a dibromoester **5** with NMR data close to those obtained from (−)sedridine. Albeit this fits with the concept of structural isomerism rather than epimerism, the question at present cannot unequivocally be

answered. The configurational problem, however, has been solved. Natural (+)sedridine has the same configuration at C-2′ as *S*(+)2-octanol, also *S* configuration at C-2 in the piperidine moiety, **8**. Simultaneously with and independently of our announcement, Cymerman Craig and his associates[3] reached the same conclusion concerning C-2′ by comparing ORD and CD curves of (−)sedridine in acidic medium with those of *R*(+)2-octanol—both were plain negative. Similarly, (+)allosedridine hydrochloride gave a Cotton effect in the same sense as *S*(+)2-octanol. Details of this work were published recently,[4] together with Dutch authors. Also, a combined chemical and ORD–CD study[3,2] on the absolute configuration of (+)conhydrine gave direct proof concerning the propanol carbon as being *R*.

As a complementary piece of evidence a derivative of (−)allosedridine was subject to an X-ray study. The D-acetylleucinate of (−)allosedridine was obtained in crystalline form from the mother liquor of (−)sedridine D-acetylleucinate. The base was then converted into (−)2-*p*-nitrophenyl-6-methyl-3,4(1,2-piperido)oxazine **9**, m.p. 128–130°, $[\alpha]_D$ 50·87°, in DMF. The racemic form of the same was described to have[13] m.p. 110–112°; a mixture of equal amounts of the (−) and (+) antipodes now showed the same m.p. The levorotatory form has been studied by X-ray by one of us.[5]




**9**




**10**

The crystals are monoclinic, with $a = 22{\cdot}506$, $b = 8{\cdot}089$, $c = 8{\cdot}442$ Å, $\beta = 108{\cdot}05°$, space group *C*2. Three-dimensional intensity data were collected with a Picker and a G.E. XRD-5 diffractometer, and direct methods were used to solve the structure. The correct absolute configuration was determined from the anomalous scattering of the oxygen atoms by performing parallel refinements for both possible configurations. The final *R* value for 1654 observed reflections for the correct absolute configuration was 0·0381, while for the opposite configuration *R* was 0·0385. The analysis shows that the molecular structure is as illustrated in Fig 2, with configuration *R* at the Me-carrying C atom, and *S* at the other two asymmetric carbon atoms in agreement with structure **9** and not its antipode. Full details of the structure analysis will be published elsewhere.

The X-ray study indicates that ring junction is *trans* and that both the methyl and the aryl groups are equatorial. The same conformation was deduced from NMR data for both racemic piperidooxazines, by Phillipsborn, *et al.*[13] Therefore, all chemical and spectral data are now in full agreement, and the configurations of the four stereoisomers of 2-pipecolyl methyl carbinol are described as follows: (+)sedridine 2*S*:2′*S* (structure **8**) (−)allosedridine 2*S*:2′*R* structure **10**. Therefore (−)sedridine is the 2*R*:2′*R* and (+)allosedridine the 2*R*:2′*S* modification. In other terms, (+)sedridine is threoid while (+)conhydrine, 2*S*:1′*R* pipecolyl ethyl carbinol is erythroid. Accordingly, recent biosynthetic work by Leete and Spenser, reviewed[33] by Spenser, has proved the acetate route for conhydrine, and lysine to be precursor of sedridine.

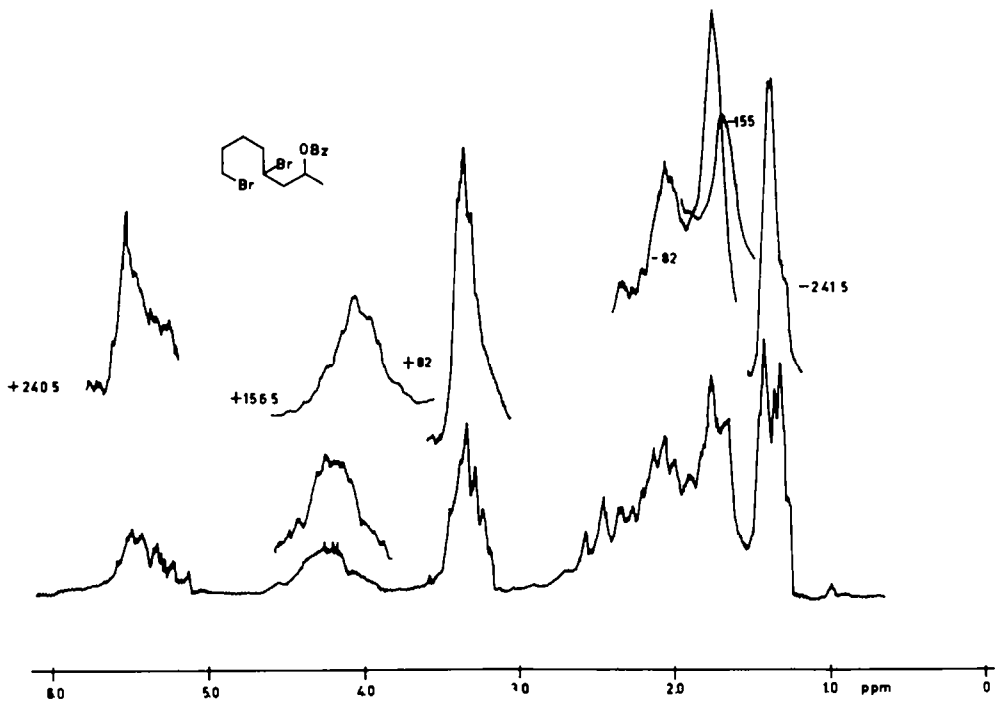



FIG 1. 60 Mc NMR spectrum of 4,8-dibromo 2-octyl benzoate, **5**, before and after double irradiation

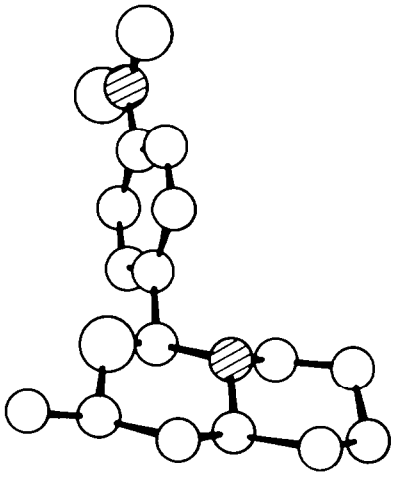
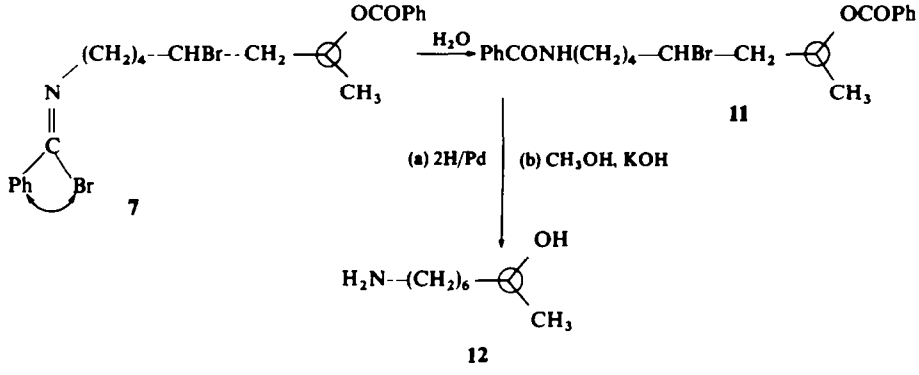


FIG 2. A view of the (−) 2-*p*-nitrophenyl-6-methyl-3,4 (1,2-piperido) oxazine molecule, as established by X-ray diffraction. The large open, hatched, and small open circles represent O, N, and C atoms respectively

Returning to the products of the von Braun reaction, as mentioned before, formation of benzonitrile is preceeded by that of phosphorus oxybromide, therefore the first step probably does not follow a concerted pattern. An iminium salt was trapped recently[34] in an analogous treatment of benzoyl coniine with carbonyl bromide, for example, that on heating gave the end products of the von Braun reaction. During our work on N,O-dibenzoyl sedridine we isolated by vacuum distillation a high-boiling bromo compound which was easily hydrolized to an amide ester with IR data and approximate analytical figures close to 4-bromo-8-benzamido-2-octyl benzoate (or to the 8-bromo-4-benzamido isomer). NMR showed two methine protons at $\delta$ 5·5(m) and 5·20(q) for H—C—Br and H—C—O but not at 3·30 expected for $H_2Br$. Hydrogenolysis, followed by hydrolysis led to X-amino-2-octanol, purified as hydrochloride[35] which had one C—$CH_3$(d) signal in NMR, in agreement with a terminal nitrogen function of (−)8-amino 2-octanol, **12**. By inference, the bromo ester amide should be 4-bromo-8-benzamido 2-octyl benzoate, **11**, probably being formed from the bromoalkyl imidoyl bromide, **7**.




Imidoyl bromides were supposed to be intermediates in von Braun reaction, for chloroimidoyl chlorides had been isolated from reaction of cyclic amides and phosphorus pentachloride.[36] However, **7** cannot be a precursor for **5** since it endures prolonged heating and distillation. The structural isomer of **7**, with nitrogen function at C-4 is not likely either, for such a derivative was isolated[32] as a by-product from a von Braun reaction on dibenzoyl conhydrine. The alternatives that remain are (i) that the *anti*-isomer of **7** could undergo *anti*-elimination while the *syn*-form is unable to do so and (ii) that bromoalkyl imidoyl bromides are not intermediates just by-products of the reaction while the fragmentation proper involves a nitrilium salt. In view of the not-too-high rotational barrier around C=N bonds we are more inclined to the second concept. At any rate, further investigations are in progress in order to make the von Braun amide degradation competitive to the Hofmann methylation procedure. Carbonyl bromide[37] recently used for replacing phosphorus pentabromide makes this degradation milder, also enabling a more profound study of its mechanism.[34]

## EXPERIMENTAL

M.p's were taken with an Electrothermal m.p. apparatus in an open capillary tube and are uncorrected.

IR spectra were taken on a Beckman IR-4 spectrophotometer, mostly in KBr pellets, while liquids were measured between NaCl plates. ORD curves were taken with JASCO model ORD/UV-5 in 1 cm cells. Optical rotatory values were obseerved on Schmidt-Haensch visual type of polarimeter, cell length 10 cm, on the sodium D line. NMR spectra were measured on Varian-60 spectrometer with model V-6058 spin decoupler. X-ray data were collected with a Picker diffractometer. Details of this technique will be published elsewhere, together with detailed measurements of bond lengths and bond angles.

*(+)and(−) Picolylmethylcarbinols* were separated as described in a previous paper.[11] Checking of optical purity was attempted according to Mislow's ideas[25,39] on diastereotopic signals. First, NMR of the adduct of optically active carbinol with (+) α-naphtyl ethylamine according to Pirkle *et al.* was taken in fluorotrichloromethane[38] as solvent. This showed for (−)PMC a methine proton resonating at 256 c/s at 60 Mc while the dextrorotary form had the same quartet centered at 259 c/s; *J* 6·2 c/s in both cases. δ is however too small to allow precise integrations. Therefore, a resolved (−)PMC$[\alpha]_D$ −41·57° was acylated with optically pure *R*(−)methylmandelyl chloride and the NMR spectrum taken in chloroform-d. Following table indicates the chemical shifts of the diastereomeric esters, the last column δ in c/s. Peak $H_B$ was chosen for integration showing that the mandelic ester and by inference the (−)carbinol we started from, are 87% optically pure. Therefore the ideal $[\alpha]_D$ value not attainable by resolution procedures was calculated[40] as 47·78° for PMC.

| Signal | O-Methylmandelyl (−) PMC ppm | (+) PMC ppm | Δδ ppm |
|---|---|---|---|
| H − 2′ (in PMC) | 5·51 (q) | 5·41 (q) | 0·10 |
| H − α (in the mandelyl moiety) | 4·68 (s) | 4·78 (s) | 0·10 |
| $OCH_3$ | 3·26 (s) | 3·31 (s) | 0·05 |
| C—$CH_3$ | 1·25 (d) | 1·13 (d) | 0·12 |

S(+)1-(2-*Pyridyl*)-2-p-*nitrobenzoyloxypropane*. (+)PMC (20 g, 0·146 mole) were mixed with *p*-nitrobenzoyl chloride (29·6 g, 10% excess) under cooling. Once the exothermic reaction was over the mass was heated on a steam bath for 2 hr, and then treated with 25% $KHCO_3$aq and extracted 3 times with a total of 200 ml chloroform. The extracts were combined, dried ($MgSO_4$) and evaporated to give 37 g (88%) crude, $[\alpha]_D$ +88·7° (*c*, 4·98, DMF). Recrystallization from 55% aqueous MeOH then gave 20 g pure product, m.p. 49–49°; $[\alpha]_D^{20}$ +106·23° (*c*, 3·5, DMF). (Found: C, 63·19; H, 5·10; N, 10·02; $C_{15}H_{14}N_2O_4$ requires: C, 62·93; H, 4·89; N, 9·78%); IR, 1720 (ester CO, 1575, 1595 (py) 1530 ($NO_2$), 720 $cm^{-1}$; NMR, δ, 8·56, 8·2 (4, ar); 7·78–7·00 (m, 3, py; 5·56 (q, 1, H—CO—: 3·23 (d, 3, $CH_3$); ORD curve (*c*, 1·9, dioxan) is plain positive $[\Phi]_{650}$ +195·6; $[\Phi]_{589}$ +229·51; $[\Phi]_{500}$ +344·68; $[\Phi]_{400}$ +654·76.

The *racemic* ester prepared in the same manner has m.p. 66–67°.

The salt of this (±) ester with *p*-nitrobenzoic acid, m.p. 130°. (Found: C, 58·40; H, 4·16; N, 9·00; $C_{22}H_{19}N_3O_8$ requires: C, 58·40; H, 3·98; N, 9·28%), has the tendency towards spontaneous resolution in MeOH when inoculated with the optically active salt. The first crop shows after three subsequent recrystallizations $[\alpha]_D^{20}$ +37·0 (*c*, 3·3, DMF) while the optically pure salt has $[\alpha]_D^{20}$ +57·44°, so its optical purity is about 64%.

1-(2-*Pyridyl*)-2-p-*nitrobenzoyloxypropane* N-*oxide*, **1b**

To the dextrorotatory *p*-nitrobenzoic ester of PMC (7 g, 0·0244 mole) dissolved in glacial AcOH (50 ml) 30% $H_2O_2$ (6 ml, 0·0528 mole) was added drop by drop. Finally, the mixture was heated in an oil-bath at 75–80° with stirring. After 3 hr 30% $H_2O_2$ (5 ml, 0·0441 mole) was added and the whole kept at the same temp for 12 hr. Then it was evaporated on a Rotavapor to near-dryness, diluted with water and again concentrated. Finally, the solid ppt was taken up in chloroform, washed with 10% $KHCO_3$, dried ($MgSO_4$) and evaporated to give yellowish colored N-oxide **1b** (6 g, 81·2%). Recrystallization from EtOAc afforded the pure product, m.p. 133–135°, $[\alpha]_D$ +178·76° (*c*, 1·85, DMF). (Found: C, 60·07; H, 4·73; N, 9·13;

$C_{15}H_{14}N_2O_5$ requires: C, 59·55; H, 4·63; N, 9·27%); IR, 1238 ($\overset{+}{N}$—O), 1610 (py), 1720 $cm^{-1}$ (CO, ester); NMR shows band width 27 c/s for $\delta$ 6·43 (H-pyridine) as compared with the tertiary amino ester, band width 70 c/s; ORD curve is plain positive. The *racemic* amineoxide **1b** melts at 144–145°.

1-(2-*Pyridyl*)-2-*propanol amineoxide*, **1a** was prepared by the same technique. From (+)PMC (2·4 g) in glacial AcOH (12 ml) and 30% $H_2O_2$ (6 ml) 2·3 g (85%) of **1a**, m.p. 47–48° were obtained and purified by distillation, b.p. (0·001 mm) 165°. (Found: C, 62·29; H, 7·28; N, 8·47; $C_8H_{11}NO_2$ requires: C, 62·74; H, 7·19; N, 9·15%); IR, 3350 (OH), 1620 (py), 1240 $cm^{-1}$ (N—O).

NMR spectrum is very similar to that of PMC, except for $\delta$ 8·25 (1, H-6) and 7·3 (3, H-3·4 and 5) of smaller band width (25 c/s). The ORD curve (*c*, 4·06, EtOH) is plain positive, $[\Phi]_{650}$ +59·35; $[\Phi]_{589}$ +74·42; $[\Phi]_{500}$ +110·26; $[\Phi]_{400}$ +202·35; $[\Phi]_{350}$ +205·23.

*Polonovski rearrangement of* **1b** *into* **2**

To 1·02 g (0·01 mole) of $Ac_2O$, N-oxide **1** (0·302 g, 0·001 mole) was added with stirring, in a flask equipped with a $P_2O_5$ tube. Two more portions of $Ac_2O$ are being added and then samples (0·2 ml) were withdrawn at regular intervals and optical rotatory values measured after being diluted to 2 ml each in DMF. The reaction was complete after 3 hr when $\alpha_D$-values did not decrease any longer. The product, 0·305 g (88·3%) crystals of the mixed ester of 1-(2-pyridyl)-1,2-propandiol, was isolated by evaporating excess $Ac_2O$ at 30° and 1 mm pressure, and washing the crystalline residue with cold 25% $KHCO_3$. m.p. 140–141°; $[\alpha]_D^{20}$ −8·91 (*c*, 2·8, DMF). (Found: C, 59·06; H, 4·55; $C_{17}H_{16}N_2O_6$ requires: C, 59·30; H, 4·65%); IR, 1730, 1720 (C=O), 1210 $cm^{-1}$ (O—C); NMR, in addition to aryl and pyridyl protons, $\delta$, 5·62 (*q*, 1, H-2), 4·60 (d, *J*, 6 c/s, **1**); 3·38 (s, 3, Ac-Me); 1·21 (d, 3, C—$CH_3$). ORD (*c*, 2·8, DMF) was plain positive: $[\Phi]_{650}$ −46·2; $[\Phi]_{589}$ −30·77; $[\Phi]_{500}$ −2·45; $[\Phi]_{450}$ +3·07.

This compound **2** was converted by the same technique as described above into the amineoxide and subjected to Polonovski rearrangement was attempted. This failed, thus confirming Boekelheide and Lynn's[26] views according to which *two* hydrogens in the side-chain are required for such a reaction. No 1,1-diacetoxy 2-*p*-nitrobenzoyloxypyridine could be detected.

2-(D-2-*methoxypropionyl*) *pyridine*. 3. D(−)Ethyl lactate (11·8 g, 0·1 mole) was methylated with MeI (142 g, 1 mole) in the presence of $Ag_2O$ added in portions (6 × 20 g, 0·5 mole) as described by Levene and Marker,[41] to D(−)ethyl 2-methoxypropionate, $[\alpha]_D$ −76·64° (homogeneous), reported value $[\alpha]_D$ −56·3°.

A soln of n-BuLi (0·48 g, 0·0075 mole) in hexane (3 ml) was added to a soln of 2-bromopyridine (1·1 g, 0·007 mole) at −65° in a $N_2$ atm with mechanical stirring. After 20 min D(−)-ethyl 2-methoxylactate (0·9 g, 0·0068 mole) in anhyd ether (10 ml) was slowly added to the dark brown soln, then kept stirring for another 2 hr at −65° and finally let it warm up to room temp. Decomposing with water (30 ml) was followed by removal of excess ether, acidification of the aqueous soln with 2N HCl, and finally extraction of unchanged ester by ether. The soln then was basified with 10% NaOH and extracted with chloroform to give, upon evaporation, 0·8276 g, oily residue. Distillation under 0·05 mm at 66° afforded 0·6434 g (57·4%) of a pale yellow liquid, that became crystalline (upon cooling to −35°) m.p. 40–45°. Purification of the *ketone* by GLC. (Autoprep, model 700, 20% Apiezon N Column on Chemosorb W, 2′ × 1·4″) temp 170°; injector 190°, detector 220°; flow rate 60 ml/min). Retention time: 2-bromopyridine, 1·76 min; *ketone*, 4·35 min $[\alpha]_D$ −62·70 (*c*, 5·91, $CHCl_3$). (Found: C, 65·24; H, 6·70; N, 8·56. $C_9H_{11}NO_2$ requires: C, 65·44; H, 6·71; N, 8·48%); IR, 1704 (C=O), 1574–1598 $cm^{-1}$ (py); NMR, $\delta$, in $CDCl_3$, 8·73 (d, 1, H-6); 8·23–7·40 (m, 3, H-3, 4 and 5); 5·38 (q, 1, H-2′); 3·43 (s, 3, $OCH_3$); 1·48 (d, 3, C—$CH_3$); mass spectrum: $M^+$ 165, *m/e* 150 (M—$CH_3$); 134 (M—$OCH_3$), 78 ($py^+$); ORD, (*c*, 3·175, dioxan, 25°) $[\Phi]_{650}$ −89·64; $[\Phi]_{589}$ −92·23; $[\Phi]_{500}$ −139·01; $[\Phi]_{410}$ −233·80; a plain negative curve.

1-*Methyl*-2-(2-*methoxypropyl*)*pyridinium bromide*. PMC methyl ether methobromide. (−)PMC (5·15 g, 0·0375 mole) was dissolved in nitromethane (75 ml), and trimethyloxonium tetrafluoroborate (14·8 g, 0·1 mole) in ether (25 ml) was added drop by drop, under cooling with ice. After stirring for 2 hr under strictly anhydrous conditions the mixture was allowed to reach 20° and then it was heated for 14 hr in an oil bath at 100°. At the end, the yellow-colored soln was evaporated on a Rotavapor. 100 ml added in order to destroy excess of the reactant and stirred for 2 hr. Evaporation of MeOH yielded an oily residue, that was dissolved in 30 ml water, and an excess of KBr was added to it. After 12 hr, $KBF_4$ was filtered off and the aqueous soln evaporated *in vacuo* at 40°. The remaining salt mixture was taken up with EtOH, filtered and evaporated to give an amorphous salt, (8·85 g, 95·8%), $[\alpha]_D^{20}$ −9·20 (*c*, 5·98, DMF). (Found: Br, 32·63; $C_{10}H_{16}BrNO$ requires: Br, 32·52%). The well-crystallized tetraphenyloborate had m.p. 156–158°, upon recrystallization from acetone–water (2:1); NMR, in DMSO-$d_6$, $\delta$, 8·35 (m, 3, py);

7·90 (m, **20**, phenyl); 4·19 (s, **3**, $NCH_3$); 3·75 (q, **1**, H-2'); 3·28 (s, **3**, $OCH_3$); 3·16 (d, **2**, $H_2C$-1'), 1·20 (d, **3**, C—$CH_3$). ORD (c, 4·06, EtOH, 25°) $[\Phi]_{650}$ −3·633; $[\Phi]_{589}$ −5·56; $[\Phi]_{500}$ −16·36; $[\Phi]_{400}$ −28·46; $[\Phi]_{370}$ −19·07; $[\Phi]_{350}$ −22·70; $[\Phi]_{325}$ +10·60.

*Reduction of methoxy ketone* **3** *to 2-(2-methoxypropyl) pyridine*

To the levorotatory ketone **3** (0·330 g, 0·002 mole) in ethylene glycol (15 ml), KOH (380 mg, 0·0068 mole) and 85% hydrazine hydrate (2·7 ml) were added and the whole was heated to 120° for 6 hr. The hydrazone was meanwhile formed and decomposed. Finally, to the cooled mixture 10 ml cold water and 25 ml $CHCl_3$ were added in a separatory funnel and the aqueous layer extracted two times, with 10 ml chloroform each time. Combined extracts were dried ($MgSO_4$) and evaporated to afford 0·450 g of a yellowish oil. Last traces of solvent were removed by vacuum, distillation under 1 mm pressure at 60–70° of the residue gave 0·234 g (77%) of 2-methoxypropyl pyridine, that showed a straight line in the ORD, indicating complete racemization; IR, 1575, 1598 (pyridine), 760, no CO was left at 1704 $cm^{-1}$; NMR, in chloroform-d, $\delta$, 3·70 (s, $OCH_3$), showing no loss of the ether bond; 4·11 broad m, **1**, H-2'); 2·86 (d, $C\underline{H}_2$); 1·25 (d, **3**, C—$C\underline{H}_3$) as expected for the methyl ether of PMC. Its methobromide gave IR and NMR spectra which were superimposable upon those of the product obtained from PMC upon methylation. Unfortunately, in lack of optical rotation no configurational assignments could be made.

Attempts to deoxygenate **3** *via* the ethylene thioketal have failed.

(+)*Sedridine and* (−)*sedridine*

Catalytic hydrogenation of (+) and (−)PMC was carried out as reported in previous papers.[11,17,24] Vacuum sublimation at 0·001 mm pressure and room temp allowed separation of the somewhat more volatile sedridine from its epimer.[17] Final purification passed through the L or D acetyl leucinates, as described previously.[11]

(−)*Allosedridine and* (+)*allosedridine*

The acetone mother liquors of precipitation of (−)sedridine N-acetyl D-leucinate were evaporated, the crystalline residue was recrystallized from acetone–MeOH and the pure product collected, m.p. 169–170°, $[\alpha]_D$ −18·7° (*c*, 1·635, MeOH).

Liberation of (−)allosedridine with ice-cold $K_2CO_3$aq has followed the technique we applied for (−)sedridine, gave the base, m.p. 59–60°, $[\alpha]_D$ −17·2° (*c*, 3·925, EtOH). Beyerman *et al.* reported[4] for the specimen, obtained on resolution of (±)allosedridine with 6,6'-dinitro-2,2'-diphenic acid, m.p. 61–62°, $[\alpha]_D$ −17·5° (in EtOH); Schöpf *et al.* recorded[12] m.p. 62–63° $[\alpha]_D$ +16·2° ±0·5 in MeOH) for a product obtained with D(−)dibenzoyltartaric acid; IR, 3300, 2930, 2850, 1445, 1375, 1335, 1200, 1150, 1120, 1100, 1055, 930, 920, and 900 $cm^{-1}$; NMR, in chloroform-d, $\delta$, 4·05 (m, **1**, H-2'); 3·85 (s, **1**, OH) and 3·53 (s, **1**, NH), both disappearing upon addition of $D_2O$; 2·88 (m, **1**, H-2); 1·70–1·37 (m, **10**, $C\underline{H}_2$); 1·15 (d, C—$CH_3$).

(2S:2'S)O,N-*dibenzoyl*(+)*sedridine*, **4**

To a soln of (+)sedridine (69, 0·042 mole), $[\alpha]_D$ +27·3°, purified through the N-acetyl L-leucinate in dry pyridine (60 ml) benzoyl chloride (11·8 g, 0·084 mole) was added dropwise while cooling with ice. After 10 min the mixture was allowed to warm up to room temp, and kept stirring for 12 hr. Then water (200 ml) was added and the mixture extracted 5 times with a total of 300 ml chloroform, the combined chloroform extracts were washed 7 times with 60 ml 20% $H_2SO_4$ two times with 50 ml water, finally 7 times with 25% $KHCO_3$aq (70 ml), dried ($MgSO_4$). Evaporation to dryness gave yellow colored oily residue (12·8 g) that upon addition of n-hexane became crystalline, 10·6 g product (73·4%). Recrystallization from 65% EtOH afforded 9·7 g (66%) pure O,N-dibenzoyl sedridine, m.p. 101–103° $[\alpha]_D$ −13·6 (*c*, 1·535, $CHCl_3$). (Found: C, 75·20; H, 7·20; N, 4·00. $C_{22}H_{25}NO_3$ requires: C, 75·18; H, 7·17; N, 3·99%); IR, 2930, 1715 (CO ester), 1630 (CO, amide), 1425, 1375, 1275, 710, 700 $cm^{-1}$; NMR, in chloroform-d, $\delta$, 8·00 and 7·40 (m, **10**, aromatic), 5·05 (m, **1**, H-2') 3·0 (m, **1**, H-2); 2·05 (t, **2**, H-6); 1·70 (m, **8**, H-3, 4, 5); 1·37 (d, 3, C—$C\underline{H}_3$). Mass spectrum, $M^+$ 351, *m/e* 246, 228, 199, 188, 187, 151, 124, 105, 97 and 77. ORD (dioxan, *c*, 2·0, 25°, shows a plain negative curve.

2R:2'S(+)O,N-*Dibenzoyl allosedridine, Dibenzoyl*-**10**

(+)Allosedridine (2 g, 0·01395 mole) $[\alpha]_D$ +15·4, was dissolved in dry pyridine (20 ml) and benzoyl chloride (3·9 g, 0·0278 mole) was added. The reaction was worked up as described for the sedridine derivative to give 3·33 g (68%) dibenzoyl allosedridine, m.p. 97–100°, upon recrystallization. $[\alpha]_D^{25}$ +75·6 (*c*, 1·84, EtOH). (Found: C, 75·40; H, 7·10; N, 4·0%); IR, 2940 (CO, ester), 1625 (CO, amide, 1430, 1280,

715 $cm^{-1}$; NMR, in chloroform-d, $\delta$, 8·00–7·46 (m, **10**, ar); 5·00 (m, **1**, H-2'); 3·16 (m, **1**, H-2); 2·13 (t, **2**, H-6); 1·60 (m, **8**, H-1', 3, 4, 5); 1·41 (d, **3**, C—$CH_3$).

The *levorotatory* allosedridine was worked up in the same manner leading to a product, $[\alpha]_D$ −76·1 (*c*, **1**, EtOH).

2S:2'S:6R(−)2-p-*Nitrophenyl-6-methyl-3,4(1,2-piperido)oxazine*, **9**

Levorotatory allosedridine (1·0 g, 0·007 mole) $[\alpha]_D$ −18 was dissolved in chlorobenzene (50 ml) and after adding *p*-nitrobenzaldehyde (1·60 g, 0·07 mole), the mixture was refluxed in a Dean–Stark separator and worked up as previously described.[17] The crystalline product, m.p. 130°, 1·1 g (60% yield) did show neither OH nor CO absorption in the IR, however, it has Bohlmann bands at 2860(m) 1795(m) 2755(m) and 2725 $cm^{-1}$(w) diagnostic of *trans*-quinolizidines; NMR, $\delta$, 8·30–7·65 (pair of d, **4**, aromatic), 4·55 (s, **1**, H-2); 3·72 (q, *J* 8 c/s, with further splitting, **1**, H—CO); 2·55–2·00 (m, **2**, H-6'); 1·7–1·3 (m, **8**, H-5, 3',4',5'), 1·2 (d, *J* 7 c/s, **3**, C—$CH_3$).

Practically the same NMR data were reported[13] for the piperido oxazine derivative of racemic allosedridine. (Found: C, 65·90; H, 7·14; N, 10·09. $C_{10}H_{20}N_2O_3$ requires: C, 65·19; H, 7·30; N, 10·14%); $[\alpha]_D^{20}$ −50·87° (*c*, 1·55, DMF).

*The 6-epimer* was prepared from 1 g (−)sedridine, purified *via* the N-acetyl-D-leucinate, $[\alpha]_D^{20}$ −28°, in analogous manner, yield 1·16 g (60%) m.p. 60–62°, in a mixture with equal amount of the (−)form, m.p. 111° $[\alpha]_D$ +62·51° (*c*, 1·49, chloroform; +68·50 (*c*, 1·44, DMF). (Found: C, 64·92; H, 7·31; N, 10·11%). In the IR spectrum Bohlmann bands appeared at 2860(m) and 2800 $cm^{-1}$(m).

*Von Braun reaction, with* N,O-*dibenzoylsedridine*

A. *Products isolated upon vacuum distillation.* To O,N-dibenzoylated natural sedridine (8 g, 0·0228 mole $[\alpha]_D$ −13·6, $PBr_3$ (6·16 g, 0·0228 mole) was added, while cooling with ice and stirring. Then drop by drop, $Br_2$ (3·63 g, 0·0228 mole) was added that converts the whole to a viscous mass. This was then distilled, first under 20 mm from an oil-bath of 80° and the distillate trapped by a cool-finger (acetone–Dry Ice); $POBr_3$ (4·56 g, 86%) distilled over. Then distillation was continued under 0·05 mm from a bath heated to 90–120°, to give 1·85 g (78%) benzonitrile, together with some carbonyl compound, (IR, 1780 $cm^{-1}$, benzoyl bromide) which was removed by shaking with $KHCO_3$ aq. The third fraction, collected at 130–150° (bath), consisted of 4·5 g (50%) 4,8-dibromo-2-octyl benzoate, **5**, IR, no absorption around 1630, strong band at 1720 $cm^{-1}$ (CO, ester). This fraction was taken up in ether, washed with 20% $KHCO_3$ and dried, then was ether evaporated to give an oily residue (3·9 g). TLC, on silicagel with benzene–light petroleum 1:1 showed $R_f$ 6·0 of a nearly colorless liquid of **5**, 4·0 g (44·8%, upon **4**); $[\alpha]_D^{20}$ +11° (*c*, 4/015, chloroform). (Found: C, 46·30; H, 5·50; Br, 41·80; O, 7·80. $C_{15}H_{20}O_2Br_2$ requires: C, 45·94; H, 5·14; Br, 40·76; O, 8·15%).

Mass spectrum showed $M^+$ 393·7, 391·7, 389·7 (calcd. 391·8); IR, 2980–2940, 1720 (CO, ester), 1600, 1570 (aryl), 1450, 1275, 1110 and 710 $cm^{-1}$; NMR, 60 mc in chloroform-d, $\delta$, 8·10 (and 7·47 (**5**, aryl); 5·52 (t, **1**, H-2) coupled with a methylene protons 174 c/s upfield; 5·22 (q, **1**, H-2), coupled with C—$CH_3$, 228 c/s upfield; 3·37 (m, **2**, $\underline{H}_2C$—Br), coupled with $\underline{H}_2C$ at 89 c/s upfield; 2·77–1·62 (m, **8**, H-3, 5, 6, 7); 1·32 (d, **3**, $CH_3$).

Hydrogenolysis of this product will be described separately.

B. By an alternative procedure, the crude reaction product from dibenzoyl (+)sedridine (9 g, 0·025 mole) **4**, $PBr_3$ (6·94 g, 0·025 mole) and $Br_2$ (4·09 g, 0·025 mole (was heated to 80° in an oil bath under 20 mm pressure for 3 hr, leading to distillation of 2·95 g (40%) $POBr_3$ identified by IR and hydrolysis. The reddish colored amorphous residue was subjected to IR measurements showing no absorption at 2200 $cm^{-1}$ diagnostic for nitriles, and no amide band around 1630 $cm^{-1}$ while still maintaining ester band at 1715 $cm^{-1}$ and a broad band centered at 1595 $cm^{-1}$ for C + N. Then the flask was evacuated by an oil pump and oil bath temp slowly raised to 90–110°, when a 2nd fraction was collected, mostly of benzonitrile (7·18 g, 83·2%) $\nu_{max}$ 2200 $cm^{-1}$ with some benzoyl bromide (IR, 1780 $cm^{-1}$) and $POBr_3$. The latter was hydrolyzed by shaking with $KHCO_3$ the chloroform soln, leaving 4 g (83·2%) benzonitrile in the organic solvent layer; this was isolated upon evaporation.

The residue of the second fraction was then dissolved in 350 ml chloroform, shaken with 300 ml 10% $NaHCO_3$ aq for 24 hr in order to hydrolyze acid halides, imidoyl bromides, etc. The dried ($MgSO_4$) extract was evaporated on a Rotavapor leaving behind 8·1 g crude dibromooctyl benzoate which then was purified through a BDH-silicagel column, in benzene-light petroleum 9:1 soln. The nearly colorless eluate had to be purified once more by TLC, on silicagel in benzene–light petroleum mixture (9:1), $R_f$ 4·8.

After evaporating the solvents, this residue, 4·3 g (48%) was analyzed. (Found: C, 45·60; H, 5·00; Br,

42·10; O, 7·7. $C_{15}H_{20}O_2Br_2$ requires: C, 45·94; H, 5·14; Br, 40·75; O, 8·15%); $[\Phi]_D$ +14·2° (*c*, 2·25, EtOH); +13·4° (*c*, 1·23, chloroform); $[\Phi]_D$ +14·2° (*c*, 2·25, EtOH).

*Mass spectrometry.* $M^+$ 3907, 391·7; 392·7 (calcd. 391·8), with several further fragments, similar as under (A). Distillation of this ester did not result in any changes of the mass spectrum; IR, 2950, 1720, 1600, 1570, 1450, 1275, 1110 and 710 $cm^{-1}$ close to though not superimposable, on the product obtained under (A).

For NMR see also Fig 1, indicating most signals ($\delta$, 8·10, 7·48, 5·45, 4·23, 33·36; 2·63 and 1·45) and double irradiation of same. This technique clearly revealed in the two specimina an interchange of the relative positions of HC—Br and HC—O chemical shifts, underlined. For an interpretation in terms of structural isomerism versus epimerism, see Theoretical Part.

*Conversion of* (+)*5,8-dibromo 2-octyl benzoate,* **5**, *into* S(+)*2-octanol,* **6**

Products **5** obtained on distillation (A) or by chromatographic separation (B) were submitted in an identical manner to hydrogenolysis and subsequent hydrolysis into 2-octanol, as follows.

A soln of (+)4,8-dibromo-2-octyl benzoate (1·6 g, 0·0041 mole), **5**, in 10 ml 95% EtOH was added to a suspension of Pd–C (1·85 g) and barium hydroxide octahydrate (5 g, excess) in EtOH (10 ml) presaturated with $H_2$ and shaken in a hydrogenation flask under 1 atm until uptake of $H_2$ (190 ml calcd. 182·78 ml). The soln was then filtered off the catalyst and evaporated to dryness. The mixture, which smelled after 2 octanol, was taken up in 10 ml ether in order to remove inorganic material and the ethereal extract evaporated under atmospheric pressure; IR, 1720 (strong) 3350 (OH, medium), 1600, 1560, 710 $cm^{-1}$ indicated a mixture of 2-octyl benzoate with 2-octanol; NMR, $\delta$, 8·11 and 7·47 (**5**, aryl), 5·20 (m, 1, H-2), simplifies upon double irradiation at 234 c/s upfield; 1·31 (m, 13, H-1,3,4,5,6,7) and 0·99 (d, 3, H-8); integration data are only approximate; $[\alpha]_D^{20}$ +18·0° (*c*, 1·76, chloroform), lower than reported[41] $[\alpha]_D^{20}$ −28·7 also shows contamination by the lower rotating free alcohol.

*Hydrolysis* of this ester was carried out as follows: A soln of 2-octyl benzoate (0·45 g, 0·0019 mole) (using technique (B) for isolating **5**) which contains 0·225 g KOH (0·004 mole) was refluxed for 6 hr in a $N_2$ atm. MeOH was distilled off under atm pressure using a 3" Vigreux column, then the residue taken up in ether, filtered of potassium benzoate and alkali and evaporated again to dryness. This operation had to be repeated 3 times. A colorless liquid, 0·193 g (78%) remained with strong smell after 2-octanol, m.p. (20 mm) 87°; $[\alpha]_D^{20}$ +8·1° (*c*, 2·815, chloroform). An authentic specimen from Koch–Light Co., England, showed $[\alpha]_D^{20}$ +8·6° (*c*, 5, chloroform). Phillips[42] reported $[\alpha]_D^{20}$ +8·06°. Another experiment carried out with octyl benzoate (1·8 g) from a sample prepared by Method A, in MeOH (25 ml), containing 0·9 KOH, gave 2-octanol (1·0 g) $[\alpha]_D^{25}$ +8·8° (*c*, 1·87, chloroform); ORD curve (*c*, 1·7, chloroform) is plain positive; $[\Phi]_{589}$ +11·35; $[\Phi]_{500}$ +1794; $[\Phi]_{400}$ +44·33. These fit well with those of an authentic specimen; IR, 3350, (OH); 2940, 2870, 1470, 1380, 1145 and 1115 $cm^{-1}$, superimposable on that of an authentic specimen; NMR, chloroform-d, $\delta$, 3·76 (m, **10**, H-2); 2·38 (d, 1, OH) exchanged with $D_2O$; 1·35 (broad m, **10**, $CH_2$); 1·16 (d, 3, H-1, $CH_3$) coupled with the proton at $\delta$, 3·76; 0·88 (t, 3, H-8, $CH_3$).

*Isolation of* 4*-bromo-*8*-benzamido-*2*-octyl benzoate* **7** *and its conversion into* 8*-amino* 2*-octanol,* **12**

When distillation of the products of the von Braun reaction, according to method A, was continued from a Späth tube after having separated dibromo ester **5**, a higher boiling semi-solid (5·2 g, from 9 g dibenzoyl sedridine) has been isolated. This was taken up in ether (50 ml) and shaken several times with 5% $NaHCO_3$ aq until the latter remained alkaline. Acidification of this portion afforded 0·780 g benzoic acid, m.p. 122–124°. The ethereal layer was dried ($MgSO_4$) and evaporated, to give 4·40 g of an amide as indicated by IR, 1635 cm, amide II, 1540 $cm^{-1}$, ester band 1722 $cm^{-1}$. Analytical values pointed to a compound close to brominidoyl bromide **7**, after purification by TLC, on silicagel (benzene: ethyl acetate 3:1). (Found: C, 62·78; H, 6·72. $C_{22}H_{26}NO_3Br$ requires: C, 61·25; H, 6·03%); $[\alpha]_D$ +22·89° (*c*, 4·93, dioxan); ORD curve is plain positive, $[\Phi]_{650}$ +89·60; $[\Phi]_{589}$ +98·65; $[\Phi]_{500}$ +126·75; $[\Phi]_{450}$ +154·25; $[\Phi]_{400}$ +203·25. NMR, chloroform-d, $\delta$, 8·06 and 7·35 (**10**, aromatic) 5·51 (m, 1, H—CBr); 5·2 (m, 1, H—CO); 3·91 (s, 1, NH) exchanged with heavy water; 3·31 (m, 2, H-8); 2·83 to 1·5 (envelop, 8, H-2,5,6,7); 1·36 (d, 3, $CH_3$).

*Hydrogenolysis* of benzamido bromoctyl benzoate **11** (3·5 g, 0·0081 mole) in EtOH (30 ml) over Pd–C (3·5 g) in the presence of barium hydroxide (7 g) was finished after uptake of 182 ml (1 mole) of $H_2$, within 4 hr. The filtrate of the catalyst was evaporated to dryness then ether was added to precipitate Ba compounds, then it was filtered and finally evaporated to give 2·65 g benzamidooctyl benzoate. This was

immediately hydrolyzed with 2N KOH in MeOH as given for octyl benzoate. Addition of ether to the residue several filtrations of salts and alkali and evaporations of ether gave 0·5 g (46·3%) 8-amino 2-octanol, **12**, $[\alpha]_D$ +14·91° (*c*, 1·12, chloroform); IR, 3350 $cm^{-1}$ very large, for $NH_2$ and OH; NMR, in chloroform-d, $\delta$, 4·23 (s, 2, $NH_2$); 3·93 (sextet, 1, H-2); 2·6 (m, 2, H-8); envelop, centered at 1·48 (**10**, $CH_2$) and 1·3 (d, 3, C—$CH_3$) indicating terminal position of the N function. Gabriel[35] has synthesized the racemate of **11**, reporting m.p. 80° for the *hydrochloride*. Treatment of *base* **11** with 2N HCl in MeOH gave upon evaporation and recrystallization from acetone, needles, m.p. 78°. (Found: Cl, 19·02. $C_8H_{20}ClNO$ requires: Cl, 19·55%).

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