66. *The Synthesis of a β-Batyl (Glycerol 2-Octadecyl Ether) Analogue of Cephalin, and Melting-point Data for Batyl, Chimyl, β-Batyl, and β-Chimyl Alcohol and their Derivatives.*

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A stearoyl-β-batyl analogue of cephalin has been prepared by a method previously described for the isomeric batyl analogue. The two isomers have the same m. p., but they are readily distinguished by their short *X*-ray spacings and by the ease with which the batyl analogue is dephosphorylated by acetic acid–acetic anhydride mixture. M. p. data are given for batyl, chimyl, β-batyl, and β-chimyl alcohol, and their diacetyl and ditrityl derivatives and diphenylcarbamates.

Baylis, Bevan, and Malkin [1] have described the synthesis of batyl analogues of cephalin, by the interaction of silver 2-(benzyloxycarbonylamino)ethyl phenyl phosphate and, *e.g.*, batyl 1-iodide 2-stearate. We have now prepared the β-batyl cephalin analogue by the same method using β-batyl 1-iodide 3-stearate (2-*O*-octadecylglycerol 1-iodide 3-stearate).

As explained in the above paper, these analogues are of interest in connection with the structure of plasmalogens, about which doubt still exists. The structures proposed by Klenk and Debuch [2] and by Rapport, Lerner, Alonzo, and Franzl [3] should give rise, on reduction, to batyl and β-batyl analogues of cephalin, respectively.

Table 1. *Short* X-*ray spacings of cephalins and analogues.*

Batyl and chimyl cephalin ...			5·91 w	4·86 w	4·14 vs	3·83 m	3·56 w
Cephalin			5·92 w	4·93 w	4·18 vs	3·86 m	3·6 w
β-Cephalin	5·59 s	4·64 vs	4·33 m	4·23 m	3·89 w	3·79 m	3·63 m 3·74 m
β-Batyl cephalin			5·46 w	4·68 w	4·05 vs	3·74 m	

w = weak; m = moderate; s = strong; vs = very strong.

Table 2. *M. p.s of batyl, chimyl, β-batyl, and β-chimyl alcohol and their derivatives.*

	Alcohol	Diacetyl deriv.	Dityrityl deriv.	Diphenylcarbamate
Batyl	71—72° (66°)	43° (35°)	71°	97°
β-Batyl	71 —	34 (29)	81	93
Chimyl	63 (58)	33 (24)	62	95
β-Chimyl	63	26 (18)	69	88

M.p.s of lower-melting forms in parentheses.

We find that these isomeric analogues have the same m. p. but they are readily distinguished by their short *X*-ray spacings (Table 1) and by the action of a hot mixture of acetic acid and acetic anhydride,[4] which converts the batyl analogue into batyl 1-acetate 2-stearate but fails to dephosphorylate the β-batyl isomer.

In view of the growing interest in the glycerol ethers in the lipid field, we have prepared a number of derivatives for their characterisation (Table 2). Batyl and chimyl alcohol melt too closely to their β-isomers for identification by m. p., but the former are distinguished by their consumption of 1 mol. of periodic acid,[5] and by their dimorphism. Moreover, only the β-isomers crystallise in spherulite formations, which are best seen under a microscope, between crossed nicols.

* Gupta and Kummerow (*J. Org. Chem.*, 1959, **24**, 409) have recently described an excellent method for the preparation of this alcohol in high yield.

[1] Baylis, Bevan, and Malkin, *J.*, 1958, 2962.
[2] Klenk and Debuch, *Z. physiol. Chem.*, 1954, **296**, 179.
[3] Rapport, Lerner, Alonzo, and Franzl, *J. Biol. Chem.*, 1957, **225**, 859.
[4] Bevan, Brown, Gregory, and Malkin, *J.*, 1953, 129.
[5] Stegerhoek and Verkade, *Rec. Trav. chim.*, 1956, **75**, 143.

Experimental

β-*Batyl Alcohol.**—This was first made by Davies, Heilbron, and Jones [6] by interaction of octadecyl iodide and potassium *O*-benzylideneglycerol in boiling benzene. They obtained widely varying yields and finally claimed a 71% yield of product, m. p. 62—63°. Our highest yield, by their method, was 10% of product, melting at 71°. This was improved to 30% by the use of xylene as solvent instead of benzene. We also used the benzylideneglycerol of m. p. 84° instead of the mixture of geometric isomers, m. p. 63°, used by Davies *et al.*

1,3-*O*-Benzylideneglycerol,[7] m. p. 84° (18 g., 0·1 mole), was added in portions to vigorously stirred, finely powdered potassium (3·9 g., 0·1 mole) under xylene (300 ml.), and the reaction was completed by refluxing and stirring. Octadecyl iodide (60 g., 0·175 mole) was then added in portions, and refluxing and stirring were continued for 20 hr. After cooling, potassium iodide was removed and the filtrate was evaporated under reduced pressure. The residue was distilled at $<0·1$ mm. to remove benzylideneglycerol and unchanged octadecyl iodide, and the residue (17 g.) was crystallised twice from ethanol to yield 13 g., m. p. 57—58° (Found: C, 77·9; H, 11·2. Calc. for $C_{28}H_{48}O_3$: C, 77·8; H, 11·1%).

The benzylidene group was removed by hydrolysis and by hydrogenolysis. The latter is by far the superior method.

Hydrolysis.—The benzylidene compound (11 g.) was refluxed for 70 min. in 75% aqueous ethanol (150 ml. of alcohol, 50 ml. of water) containing concentrated hydrochloric acid (11 ml.). After cooling and dilution with water, the precipitated solid was collected, washed with water, and dried. After one crystallisation from ethanol and two from ethyl acetate, there remained 7 g. of crystalline product, m. p. 71°.

Hydrogenolysis.—The benzylidene compound (1·08 g.) was hydrogenated in ethyl acetate (40 ml.) at atmospheric pressure in the presence of platinum black (0·3 g.). Crystals slowly separated during this stage. When absorption of hydrogen had ceased, the apparatus was evacuated to remove hydrogen, and the solution was warmed to dissolve the precipitated product. The catalyst was then removed and washed with solvent, and the solution was evaporated under reduced pressure to give a quantitative yield of β-batyl alcohol, m. p. 71°, unchanged on crystallisation (Found: C, 73·2; H, 12·9. Calc. for $C_{21}H_{44}O_3$: C, 73·3; H, 12·8%).

β-*Chimyl Alcohol.*—This was made in the same manner, from hexadecyl iodide. The intermediate benzylidene compound, from methanol–ethanol (1 : 1), had m. p. 38—39° (yield 30%) (Found: C, 77·3; H, 10·9. Calc. for $C_{26}H_{44}O_3$: C, 77·2; H, 10·9%). Hydrolysis or hydrogenolysis gave β-chimyl alcohol, m. p. 63° (from acetone) (Found: C, 72·2; H, 12·7. Calc. for $C_{19}H_{40}O_3$: C, 72·2; H, 12·7%). Davies *et al.*[6] give m. p. 60—61°.

β-*Batyl Monostearate.*—Stearoyl chloride (3·03 g.) was added dropwise to β-batyl alcohol (3·44 g.) in chloroform (50 ml.) containing pyridine (3 ml.) with vigorous stirring during 20 hr. Stirring was continued for a further 4 hr. and the solvent was removed under reduced pressure. The residue was triturated twice with water, separated by filtration, and dried *in vacuo*. Crystallisation from ethanol and acetone (twice) yielded colourless crystals (5·3 g., 87%), m. p. 57—59°. This product gave correct analyses for β-batyl monostearate, but from its melting behaviour we suspect the presence of a trace of the distearate. This is removed in the next stage.

*Stearoyl-β-batyl Toluene-*p*-sulphonate.*—β-Batyl monostearate (4·72 g.) was added in small portions to toluene-*p*-sulphonyl chloride (2 g.) in pyridine (14 ml.), kept at 40° for 2 hr., cooled, and poured into water. The precipitate was collected, washed with water, and dried *in vacuo*. Crystallisation from ethanol, and twice from light petroleum (b. p. 40—60°) gave crystalline *product* (4·6 g.), m. p. 70° (Found: C, 72·3; H, 10·8. $C_{46}H_{84}O_6S$ requires C, 72·3; H, 11·0%).

Stearoyl-β-batyl Iodide.—The above toluene-*p*-sulphonate (3·5 g.) was refluxed and stirred in the dark for 24 hr. in dry acetone (50 ml.) containing sodium iodide (2·25 g.). The precipitated sodium toluene-*p*-sulphonate was then removed (0·83 g., theor. 0·89 g.) and when the filtrate was cooled the iodide crystallised and was collected (3·9 g.; m. p. 60°). Crystallisation from acetone did not alter the m. p. This *compound* also exists in a form, m. p. 41—42° (Found: C, 65·2; H, 10·7. $C_{39}H_{77}O_3I$ requires C, 65·0; H, 10·7%).

β-*Batyl Analogue of Cephalin.*—Stearoyl-β-batyl iodide (2·6 g.) was added to a solution of silver 2-(benzyloxycarbonylamino)ethyl phenyl phosphate (2 g.) in boiling xylene (60 ml.) in

[6] Davies, Heilbron, and Jones, *J.*, 1934, 1232.
[7] Verkade and van Roon, *Rec. Trav. chim.*, 1942, **61**, 831.

the dark, and the mixture was refluxed and stirred for 15 min. The solution was then cooled and the precipitated silver iodide was removed (Filtercel). After removal of solvent under reduced pressure, the residue was dissolved in ether and washed with water, with half-saturated sodium hydrogen carbonate (twice), and again with water. After drying (Na_2SO_4) and removal of the solvent, there remained a low-melting solid (3 g.). This was dissolved in acetic acid–chloroform (2 : 1; 100 ml.) and hydrogenated at slightly >1 atm. pressure in the presence of a 1 : 1 mixture (1 g.) of palladium black and Adams platinum oxide. When absorption of hydrogen ceased, the apparatus was evacuated to remove hydrogen, chloroform was added to dissolve precipitated product, and the catalyst was removed and washed with chloroform. Solvents were then removed under reduced pressure at <40° with the addition of benzene to remove final traces of acetic acid. The residue was extracted thrice with boiling ether to remove impurities; there remained 1·5 g. (57%) of microcrystalline β-batyl cephalin, m. p. 198° unchanged after crystallisation from ethanol (Found: C, 67·0; H, 11·5; N, 2·0; P, 4·2. $C_{41}H_{84}O_7NP$ requires C, 67·1; H, 11·5; N, 1·9; P, 4·2%).

On evaporation of the above ethereal extract there remained 0·7 g. of material which when crystallised twice from acetone melted at 59° and analysed correctly for *β-batyl monostearate* (Found: C, 76·9; H, 12·7. $C_{39}H_{78}O_4$ requires C, 76·7; H, 12·8%). The identity was confirmed by the following preparation. Stearoyl-β-batyl iodide (0·5 g.) was refluxed for 5 hr. with silver nitrate (0·5 g.) in ethanol (20 ml.) containing water (1 ml.). The precipitated silver salt was removed after cooling (Filtercel), and on evaporation of solvent there remained 0·3 g. of residue. After crystallisation from acetone identity with the above monostearate was confirmed by m. p., mixed m. p., and analysis. The more usual reagent for this reaction, silver nitrite,[8] was not so satisfactory as the nitrate.

Action of Acetic Acid–Acetic Anhydride on Batyl and β-Batyl Cephalins.—This was carried out as described by Bevan *et al.*[4] Batyl cephalin (stearoyl) gave an 86% yield of *batyl 1-acetate 2-stearate* which is dimorphous, m. p. 41—42° (from ethanol) and 47° (from hexane) (Found: C, 75·6; H, 12·1. $C_{41}H_{80}O_5$ requires C, 75·5; H, 12·3%).

β-Batyl cephalin treated in the same manner gave a product, m. p. *ca.* 70°, which was difficult to purify and gave positive tests for nitrogen and phosphorus.

Batyl 1-Stearate 2-Acetate.—Batyl 1-stearate, m. p. 71°, was prepared by monoacylation of batyl alcohol in chloroform–pyridine as described by Malkin, Shurbagy, and Meara [9] for the the preparation of 1,3-diglycerides (Found: C, 76·9; H, 12·7. Calc. for $C_{39}H_{78}O_4$: C, 76·7; H, 12·8%). It had been previously prepared in a different manner by Stegerhoek and Verkade [5] (m. p. 71—71·5°). The stearate (0·3 g.) was heated with acetic acid–acetic anhydride (1 : 1; 6 ml.) for 8 hr., and the cold solution was poured into water and kept overnight. The precipitate was collected and crystallised from ethanol, giving 0·3 g., m. p. 40°. *Batyl 1-stearate 2-acetate* is dimorphous and has m. p. 49° (from hexane) (Found: C, 75·5; H, 12·5. $C_{41}H_{80}O_5$ requires C, 75·5; H, 12·3%). This compound was shown by *X*-rays to be different from the isomer described above; hence no migration of acyl groups occurs during the dephosphorylation.

β-Batyl 1-acetate 3-stearate was prepared for comparison by the acetylation of β-batyl monostearate. It exhibits dimorphism with m. p. 42—43° (from ethanol) and 49—50° (from hexane) (Found: C, 75·6; H, 12·0. $C_{41}H_{80}O_5$ requires C, 75·5; H, 12·3%).

Batyl Diacetate.—Batyl alcohol (0·5 g.) was heated with acetic anhydride (5 ml.) for 1 hr. The cold solution was poured into water and after some hours the precipitate (0·5 g.) was removed, washed, and dried *in vacuo* (over NaOH). After two crystallisations from methanol, and drying *in vacuo* (over H_2SO_4), there remained a transparent wax, m. p. 35°, which slowly changed to an opaque form, m. p. 43° (Found: C, 70·2; H, 11·3. Calc. for $C_{25}H_{48}O_5$: C, 70·1; H, 11·2%). Baer and Fischer [10] give m. p. 34—34·5° and 42—43° for the D- and the L-form and 34—34·5° for the DL-form.

The remaining diacetates were made similarly except that for β-chimyl diacetate it was more convenient to extract the product from aqueous suspension with ether. All exist in at least two forms, but we have not studied their polymorphism in detail and, by analogy with triglycerides, other forms would be expected.

β-Batyl diacetate, m. p.s 29° and 34° (Found: C, 70·2; H, 11·4. $C_{25}H_{48}O_5$ requires C, 70·1; H, 11·2%).

[8] Fischer, *Ber.*, 1920, **53**, 1621.
[9] Malkin, Shurbagy, and Meara, *J.*, 1937, 1409.
[10] Baer and Fischer, *J. Biol. Chem.*, 1941, **140**, 397.

Chimyl diacetate, m. p.s 24° (from methanol at 0°) and 33° (opaque form) (Found: C, 69·2; H, 10·9. Calc. for $C_{23}H_{44}O_5$: C, 69·0; H, 11·0%). Nakamiya [11] found m. p. 22°.

β-*Chimyl diacetate*, m. p.s 18° and 26° (Found: C, 69·3; H, 10·9. $C_{23}H_{44}O_5$ requires C, 69·0; H, 11·0%).

Ditrityl Derivatives.—These were made as described by Stegerhoek and Verkade [5] by the action of triphenylmethyl bromide on the alcohol in pyridine.

Ditritylbatyl alcohol, m. p. 71° (from acetone) (yield, 82%) (Found: C, 85·4; H, 8·7. Calc. for $C_{59}H_{72}O_3$: C, 85·5; H, 8·8%). Stegerhoek and Verkade give m. p. 70—71°.

Ditrityl-β-batyl alcohol, m. p. 81° (yield, 87%) (Found: C, 85·5; H, 8·8. $C_{59}H_{72}O_3$ requires C, 85·5; H, 8·8%).

Ditritylchimyl alcohol, m. p. 62° (yield, 70%) (Found: C, 85·5; H, 8·6. $C_{57}H_{68}O_3$ requires C, 85·5; H, 8·5%).

Ditrityl-β-chimyl alcohol, m. p. 69° (yield, 75%) (Found: C, 85·5; H, 8·6. $C_{57}H_{68}O_3$ requires C, 85·5; H, 8·5%).

Diphenylcarbamates.—These were made by heating the alcohols in benzene with phenyl isocyanate for 1 hr., under anhydrous conditions. The solution was then reduced to a small volume and the carbamates were precipitated by the addition of light petroleum (b. p. 100—120°). Final crystallisation was from a mixture of the latter and benzene. Thus were prepared:

Batyl diphenylcarbamate, m. p. 97° (80%) (Found: C, 72·1; H, 9·1; N, 4·9. Calc. for $C_{35}H_{54}O_5N_2$: C, 72·2; H, 9·3; N, 4·8%). Heilbron and Owens [12] give m. p. 98°; Drummond and Baker,[13] m. p. 98·5—99°; and Nakamiya,[11] 100°.

β-Batyl diphenylcarbamate, m. p. 93° (85%) (Found: C, 72·0; H, 9·2; H, 4·6. Calc. for $C_{35}H_{54}O_5N_2$: C, 72·2; H, 9·3; N, 4·8%). Davies *et al.*[6] give m. p. 83—84°.

Chimyl diphenylcarbamate, m. p. 95° (80%) Found: C, 71·5; H, 8·9; N, 5·2. Calc. for $C_{33}H_{50}O_5N_2$: C, 71·5; H, 9·0; N, 5·1%). Davies, Heilbron, and Owens [14] give m. p. 93—94°.

β-Chimyl diphenylcarbamate, m. p. 88° (90%) (Found: C, 71·7; H, 8·9; N, 4·9. Calc. for $C_{33}H_{50}O_5N_2$: C, 71·5; H, 9·0; N, 5·1%). Davies, Heilbron, and Jones [6] give m. p. 82—83°.

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[11] Nakamiya, *Bull. Inst. Phys. Chem. Res., Tokyo*, 1939, **17**, 837.
[12] Heilbron and Owens, *J.*, 1928, 942.
[13] Drummond and Baker, *Biochem. J.*, 1929, **23**, 274.
[14] Davies, Heilbron, and Owens, *J.*, 1930, 2542.