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ELIMINATION OF THE 4-HYDROXYL GROUP OF THE ALKALOIDS RELATED TO MORPHINE—IV

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Abstract—The Ullmann reaction of dihydrothebaine-ϕ and dihydrothebainone-Δ^5-enol methylether was reexamined. It was found that the yield depended on the particle size of K_2CO_3 and that the smaller the particle size, the better the yield.

IN PREVIOUS papers,[1] the Ullmann reaction of sinomenine and of thebaine derivatives with bromobenzene in pyridine solution was described. As the yields were, at first, not constant and sometimes very poor, the reaction of dihydrothebaine-ϕ was examined in detail.

As a result of many experiments it was found that the yield of the phenylether depends on the particle size of K_2CO_3 and that the smaller the particle size, the better the yield.

Consequently, the Ullmann reaction was applied to other aromatic and heteroaromatic compounds, e.g. 4-bromonitrobenzene, 2-bromonitrobenzene, 4-bromotoluene, 4-bromoanisole, 4-chloro-1,3-dinitrobenzene, 2-bromonaphthalene, 2-bromopyridine and 4-bromoquinoline.

The Ullmann reaction of dihydrothebaine-ϕ was carried out in the presence of commercial K_2CO_3 and that of dihydrothebainone-Δ^5-enol methylether with finely powdered K_2CO_3.

The results are shown in the following Tables.

The reaction of the former with 2-nitrohalogeno derivatives failed, probably because of the steric hindrance of the nitro group adjacent to the halogen.

EXPERIMENTAL

General procedure for the ether of dihydrothebaine-ϕ

A solution of dihydrothebaine-ϕ (12·54 g, 4 mmoles) in 40 cc freshly distilled dry pyridine was refluxed with the halogen compound (4·4 mmoles), Cu (2 mmoles) and commercial K_2CO_3 (4·4 mmoles) for 10 hr unless otherwise stated. The mixture was treated as described in the previous paper.[1]

The crude product chromatographed on alumina was crystallized from an appropriate solvent.

Dihydrothebaine-ϕ-(4′-nitrophenyl)-ether. The crude product was crystallized from ether yielding 9·9 g of a solvate of 4′-nitrophenylether, 52·5%, m.p. 97–108° (with foaming), $[\alpha]_D^{20}$ $-17·7° \pm 2°$ (*c*, 0·990, alc.). (Found: C, 68·68; H, 6·58; N, 5·92. $C_{25}H_{26}O_5N_2 \cdot \frac{1}{2}C_2H_5OC_2H_5$ requires: C, 68·77; H, 6·63; N, 5·94%).

The Ullmann reaction with 2-bromonitrobenzene. The reaction mixture was treated as usual. The pyridine solution was separated from the resinous products, the residue treated with chloroform and resinous products again separated. No basic substance was eluted with chloroform on chromatography over alumina.

The Ullmann reaction with 4-Chloro-1,3-dinitrobenzene. The reaction mixture was treated as described above. Only resinous products were obtained.

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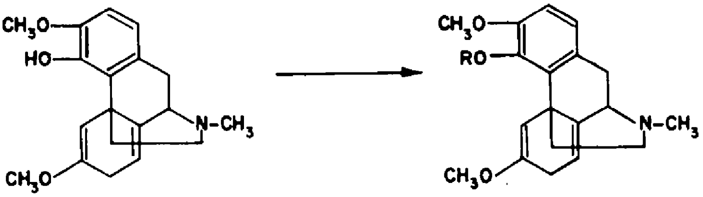
[1] Yoshiro K. Sawa, Naoki Tsuji and Shin Maeda, *Tetrahedron* **15**, 144 (1961); **15**, 154 (1961).

TABLE 1



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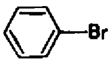
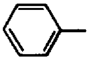
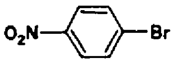
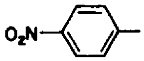
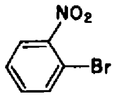
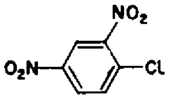
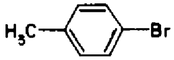
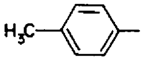
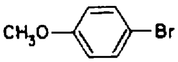
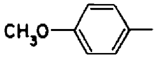
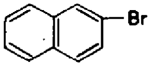
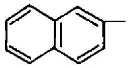
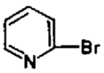
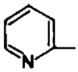
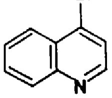
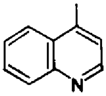
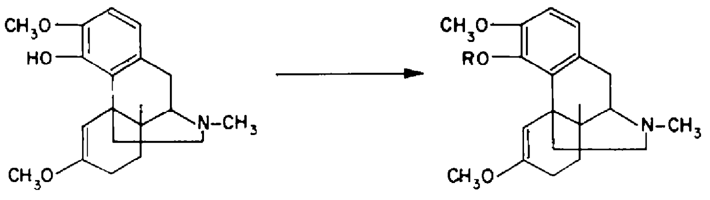
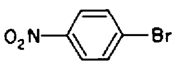
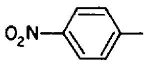
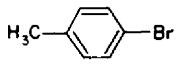
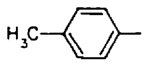
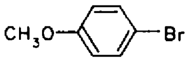
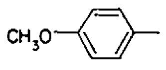
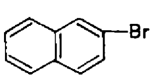
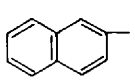
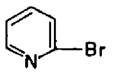
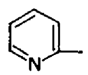
	20~50 mesh 50~100 mesh 100~200 mesh		25·5% 71% 85%
	50~100 mesh		52·5%
	50~100 mesh		Resinous product
	50~100 mesh		Resinous product
	50~100 mesh		52·4%
	50~100 mesh		51·4%
	50~100 mesh		55 %
	50~100 mesh		42·4%
	50~100 mesh		31·8%

TABLE 2



Reagent	Particle size of K_2CO_3	R	Yield
	100~200 mesh		73%
	100~200 mesh		72%
	100~200 mesh		64%
	100~200 mesh		79·5%
	100~200 mesh		80%

Dihydrothebaine-φ-(4′-tolyl)-ether. The crude product was, after chromatography, crystallized from ethanol yielding 8·468 g pure 4′tolylether, 52·4%, m.p. 159–161°; $[\alpha]_D^{28}$ +36·4° ± 2° (*c*, 1·094, alc.). (Found: C, 77·38; H, 7·30; N, 3·40. $C_{26}H_{29}O_3N$ requires: C, 77·39; H, 7·24; N, 3·49%).

Dihydrothebaine-φ-(4′-methoxyphenyl)-ether. The crude benzene eluate (8·64 g, 51·4%), m.p. 103–107°, was recrystallized from ether, m.p. 128–129°, $[\alpha]_D^{28}$ +27·1° ± 2° (*c*, 1·019, alc.). (Found: C, 73·92; H, 7·18; N, 3·33. $C_{26}H_{29}O_4N$ requires: C, 74·44; H, 6·97; N, 3·34%).

Dihydrothebaine-φ-(β-naphthyl)-ether. The mixture was refluxed for 15 hr and filtered while hot. The pyridine solution was concentrated to about 40 cc to yield the crude ether (11·2 g) on cooling. Crystallization from ethyl acetate gave pure β-naphthylether, m.p. 204–205°, 9·64 g, 55%; $[\alpha]_D^{29}$ +28·0° ± 2° (*c*, 1·059, $CHCl_3$). (Found: C, 79·03; H, 6·72; N, 3·35. $C_{29}H_{29}O_3N$ requires: C, 79·24; H, 6·65; N, 3·19%).

Dihydrothebaine-φ-(2′-pyridyl)-ether. The benzene eluate (8·08 g) was crystallized from ethyl acetate yielding 6·63 g pure product, 42·4%, m.p. 153–154°; $[\alpha]_D^{24}$ +14·7° ± 2° (*c*, 1·066, alc.). (Found: C, 73·53; H, 6·89; N, 7·17. $C_{24}H_{26}O_3N_2$ requires: C, 73·82; H, 6·71; N, 7·18%).

Dihydrothebaine-φ-(4′-quinolyl)-ether. The mixture was refluxed for 15 hr. The benzene and chloroform eluates were combined and the mixture steam distilled to remove the volatile substances. The residue was extracted with ether and again chromatographed on alumina yielding 5·6 g oily substance (31·8%) which yielded a methiodide (from ethanol), m.p. 226–227°, $[\alpha]_D^{20}$ −12·5° ± 3° (*c*, 0·624, H_2O). (Found: C, 49·87; H, 4·92; N, 3·88; I, 35·51. $C_{28}H_{28}O_3N_2 \cdot 2CH_3I$ requires: C, 49·74; H, 4·73; N, 3·87; I, 35·04%).

General procedure for the ether of dihydrothebainone-Δ⁵-enol methylether

A solution of dihydrothebainone-Δ^5-enol methylether (6·31 g, 2 mmoles) in 20 cc pyridine was refluxed for 10 hr with the halogen compound (3 mmoles) and Cu (1 mmole) in the presence of commercial K_2CO_3 (3 mmoles) which had been finely powdered in a mortar. The mixture was treated as in the case of dihydrothebaine-ϕ.

4′Nitrophenylether of dihydrothebainone-Δ⁵-enol methylether. The crude product was chromatographed on alumina to elute 8·63 g of 4′nitrophenylether which recrystallized from benzene as a pure product, m.p. 190–191° (6·37 g, 73%); $[\alpha]_D^{27}$ −110·1° ± 2° (*c*, 1·035, $CHCl_3$). (Found: C, 68·70; H, 6·68; N, 6·64. $C_{25}H_{28}O_5N_2$ requires: C, 68·79; H, 6·47; N, 6·42%).

Treatment of this compound with dil. HCl aq gave dihydrothebainone-(4′-nitrophenyl)-ether, m.p. 224·5–225·5°; $[\alpha]_D^{27}$ −9·9° ± 2° (*c*, 1·074, $CHCl_3$). (Found: C, 68·28; H, 6·33; N, 6·86. $C_{24}H_{26}O_5N_2$ requires: C, 68·23; H, 6·20; N, 6·63%).

4′-Tolylether of dihydrothebainone-Δ⁵-enol methylether. As the benzene eluate did not crystallize after standing overnight it was converted to the oxalate yielding 7·9 g of the salt, m.p. 216°dec (72%). Recrystallization from methanol–acetone raised its m.p. to 218°dec; $[\alpha]_D^{26}$ −47·9° ± 2° (*c*, 1·032, alc.). (Found: C, 67·48; H, 6·77; N, 3·09. $C_{26}H_{31}O_3N{\cdot}C_2H_2O_4$ requires: C, 67·86; H, 6·71; N, 2·83%). Dihydrothebainone-(4′-tolyl)-ether was obtained as an oil by the actionof dil. HCl aq The methiodide, crystallized from acetone, m.p. 172–173°; $[\alpha]_D^{27}$ +23·0° ± 2° (*c*, 1·027, alc.). (Found: C, 58·65; H, 6·51; N, 2·27; I, 20·88. $C_{25}H_{29}O_3N$. $CH_3I{\cdot}CH_3COCH_3$ requires: C, 58·88; H, 6·48; N, 2·37; I, 21·46%).

4′-Methoxyphenylether of dihydrothebainone-Δ⁵-enol methylether. The benzene eluate was crystallized from ethanol yielding 5·4 g 4′-methoxyphenylether, m.p. 129–131° (64%); $[\alpha]_D^{28}$ −61·8° ± 2° (*c*, 1·038, alc.). (Found: C, 73·91; H, 7·59; N, 3·49; OCH_3, 21·60. $C_{26}H_{31}O_4N$ requires: C, 74·08; H, 7·41; N, 3·32; OCH_3, 22·09%).

Treatment of this compound with dil. HCl aq gave dihydrothebainone-(4′-methoxyphenyl)-ether as an oil. The methiodide, m.p. 192–196°, crystallized from ethanol; $[\alpha]_D^{27}$ +23·0° ± 2° (*c*, 0·990, alc.). (Found: C, 55·86; H, 6·03; N, 2·85; I, 22·83. $C_{26}H_{32}O_4NI{\cdot}\frac{1}{2}H_2O$ requires: C, 55·91; H, 5·96; N, 2·51; I, 22·73%).

β-Naphtylether of dihydrothebainone-Δ⁵-enol methylether. The residue obtained from the pyridine solution was steam distilled to remove the volatile substances and the crude product was extracted with benzene. The extract was distilled under red. press. to remove bromonaphthalene and the residue was chromatographed over alumina to elute the naphthylether as an oil (7 g, 79·5%). This compound was converted to dihydrothebainone-(β-naphthyl)-ether, m.p. 207–208°; $[\alpha]_D^{27}$ +27·0° ± 2° (*c*, 1·037, $CHCl_3$). (Found: C, 78·46; H, 6·94; N, 3·26. $C_{28}H_{29}O_3N$ requires: C, 78·66; H, 6·84; N, 3·28%).

2′-Pyridylether of dihydrothebainone-Δ⁵-enol methylether. The crude product obtained from the pyridine solution was steam distilled to remove volatile products and the residue extracted with benzene. Chromatography over alumina and successive crystallization from ether gave 6·33 g 2′-pyridylether, m.p. 160–162° (sintering at 156°), 80·7%; $[\alpha]_D^{30}$ −39·3° ± 2° (*c*, 1·067, alc.). (Found: C, 73·13; H, 7·24; N, 7·25. $C_{24}H_{28}O_3N_2$ requires: C, 73·44; H, 7·19; N, 7·14%). The 2′-pyridylether was converted to a dihydrothebainone derivative as usual, m.p. 104–111°; $[\alpha]_D^{27}$ +13·1° ± 2° (*c*, 1·017, alc.). (Found: C, 67·07; H, 7·32; N, 6·87). $C_{22}H_{23}O_3N_2{\cdot}1\frac{1}{2}H_2O$ requires: C, 68·12; H, 7·12; N, 6·91%).

Acknowledgements—We are indebted to Prof. emeritus Ochiai of Tokyo University and Dr. Takeda, Director of this laboratory for valuable discussions.