708. *Further New Tropine Derivatives.*

By R. Foster, P. J. Goodford, and H. R. Ing.

The α-benzylmandelic ester of ψ-tropine and the phenyl-α-2-thienylglycollic and 9-hydroxyfluorene-9-carboxylic esters of tropine have been prepared and tested as spasmolytics. Some new derivatives of the benzilic esters of tropine and ψ-tropine have also been made and tested.

In earlier papers [1,2] the synthesis of the α-benzyl-lactic esters of tropine and ψ-tropine (originally thought to be α-methyltropic esters) was described. In continuation of this work attempts have been made to prepare the tropine and ψ-tropine esters of other disubstituted glycollic acids. The general method of preparation was transesterification, ethyl esters being used because it was found that ethyl benzilate gave yields of 70—80% in the transesterification reaction, whereas with methyl benzilate yields of only 20—30%

[1] Foster and Ing, *J.*, 1956, 938.
[2] *Idem*, *J.*, 1957, 925.

were obtained. The reaction was not always successful; thus ψ-tropine α-benzylmandelate was prepared but the corresponding tropine ester could not be obtained. On the other hand, the tropine esters of phenyl-2-thienylglycollic and 9-hydroxyfluorene-9-carboxylic acid were prepared, though in poor yields, but the corresponding ψ-tropine esters could not be obtained.

Ethyl α-benzylmandelate was prepared by the method which Burtner and Cusic [3] devised for the preparation of α-phenyltropic acid, but which Zaugg [4] later proved to give α-benzylmandelic acid by a molecular rearrangement during the reaction of a β-amino-αα-diphenylpropionic ester with nitrous acid.

The benzilic esters of tropine and ψ-tropine were found by Benda and Kraup [5] and by Kreitmair [6] respectively to possess high atropine-like activity. We have included them in our studies and have made and tested their methiodides, ethiodides, and hexamethylene and decamethylene di-iodides.

A summary of the pharmacological results is given in Table 1, in which are included earlier results on the tropine and ψ-tropine esters of α-benzyl-lactic acid and some derivatives of them.

TABLE 1. *Approximate spasmolytic and mydriatic activities of tropine and ψ-tropine esters in terms of atropine sulphate.*

Compound	Spasmolytic activity	Mydriatic activity
Atropine sulphate	1	1
Lachesine	1·5	1
Tropine esters		
α-Benzyl-lactic perchlorate	0·2	0·1
,, methiodide	1	1
,, benzylochloride	0·01	—
Benzilate hydrochloride	1·5 L	0·4
,, methiodide	1	—
,, ethiodide	1	—
Bisbenzilate hexamethylene di-iodide	0·2	0·1
,, decamethylene di-iodide	0·1	—
Phenyl-2-thienylglycollate (free base)	0·7 LP	—
9-Hydroxyfluorene-9-carboxylate (free base)	0·3 L	—
,, ,, ,, methiodide	0·2 LP	—
ψ-Tropine esters		
α-Benzyl-lactate hydrochloride	0·1	0
,, methiodide	1·5	0·25
,, benzylochloride	0·1	—
α-Benzylmandelate (free base)	0·15	—
,, methiodide	0·4	—
Benzilate hydrochloride	0·4	0·2
,, methiodide	1	—
Bisbenzilate hexamethylene di-iodide	0·1	0·03
,, decamethylene di-iodide	0·3	—

L denotes a long-acting but reversible effect.
LP denotes a permanent or very prolonged effect.

It will be seen that both replacement of one phenyl group in tropine benzilate by 2-thienyl and linking of the phenyl groups in the *oo'*-positions reduce spasmolytic activity; in this connexion it has been reported that the phenyl-2-thienylglycollic ester of 2-diethylaminoethanol [7] is 1·5 times as active, but the 9-hydroxyfluorene-9-carboxylic ester [8] one-eighth as active, as the corresponding benzilic ester (rabbit intestine). Lands [7] found that the diphenyl- and the phenyl-2-thienyl-acetic ester of tropine were 6 and 22% as active respectively as atropine (rabbit intestine) so that the introduction of the

[3] Burtner and Cusic, *J. Amer. Chem. Soc.*, 1943, **65**, 262.
[4] Zaugg, *J. Amer. Chem. Soc.*, 1950, **72**, 3001.
[5] Benda and Kraup, *Wien. Klin. Wochenschr.*, 1954, **66**, 445.
[6] Kreitmair, *Klin. Wochenschr.*, 1936, **15**, 676.
[7] Lands, *J. Pharmacol.*, 1951, **102**, 219.
[8] Lands, Hoppe, Lewis, and Ananenko, *ibid.*, 1950, **100**, 19.

α-hydroxy-group into the acyl group of these esters increases activity (cf. Jowett and Pyman [9]) but much more so in the diphenyl- than in the phenyl-2-thienyl-substituted acyl group.

The partially irreversible action of tropine hydroxyfluorenecarboxylate methiodide was unexpected and may be due to a toxic effect upon the ileum since quaternary spasmolytics are usually shorter-acting than their parent tertiary bases. It will be noticed that in accordance with previous experience [10] methiodides are usually more active than their parent bases, the exception in Table 1 being tropine benzilate methiodide.

It is noteworthy that linking of the nitrogen atoms of tropine benzilate by a hexa- or deca-methylene chain produces a striking decrease in spasmolytic activity, whereas Kimura and Unna [11] describe the spasmolytic activity of decamethylenebisatropinium di-iodide as identical with that of atropine.

Experimental

Pharmacology.—Two pharmacological tests were used. Mydriatic activity was estimated on the mouse eye by Pulewka's method [12] as modified by Ing, Dawes, and Wajda.[13] Spasmolytic activity against acetylcholine or carbachol as spasmogenic agents was estimated on isolated guinea-pig ileum. Lachesine (2-benziloylethyldimethylethylammonium chloride [14]) was found to be more convenient than atropine as the standard spasmolytic because it is more rapidly washed out of the isolated ileum and consequently more estimations can be made on one piece of ileum than with atropine. Lachesine was found to be 1·5 times as potent a spasmolytic as atropine.

Table 2. *Derivatives of tropine and ψ-tropine benzilates.*

Ester	M. p.	Solvent	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Tropine benzilate	150° [a]	C_6H_6 or EtOH	$C_{22}H_{25}O_3N$	—	—	—	—
,, hydrochloride	220	PrOH or dioxan	$C_{22}H_{25}O_3N$,HCl	68·2	6·8	68·2	6·7
,, *methiodide*	220	MeOH	$C_{23}H_{28}O_3NI$	56·0	5·6	56·0	5·7
,, *ethiodide*	240	,,	$C_{24}H_{30}O_3NI$	56·8	6·1	56·7	5·9
Bistropine benzilate *hexamethylene di-iodide*	dec. 230—240	EtOH–EtOAc (4 : 1 v/v)	$C_{50}H_{62}NI_2,H_2O$	56·8	6·0	56·8	6·0
Bistropine benzilate *decamethylene di-iodide*	dec. 170	ditto	$C_{54}H_{70}O_6N_2I_2,H_2O$	58·3	6·4	58·2	6·5
ψ-Tropine benzilate	156 [b]	EtOH (70% v/v)	$C_{22}H_{25}O_3N$	—	—	—	—
,, hydrochloride	225 [c]	EtOH–EtOAc (2 : 3 v/v)	$C_{22}H_{25}O_3N$·HCl	68·0	6·6	68·2	6·7
,, *methiodide*	240	MeOH	$C_{23}H_{28}O_3NI$	55·7	5·4	56·0	5·7
,, *ethiodide*	240	MeOH	$C_{24}H_{30}O_3NI$	56·5	5·5	56·7	5·9
Bis-ψ-tropine benzilate *hexamethylene di-iodide*	dec. 230—240	MeOH	$C_{50}H_{62}O_2N_2I_2,2H_2O$	55·7	6·0	55·8	6·1
Bis-ψ-tropine benzilate *decamethylene di-iodide*	dec. 195	EtOH (90% v/v)	$C_{54}H_{70}O_6N_2I_2,2H_2O$	57·5	6·5	57·2	6·5 [d]

[a] Hromatka, Csoklich, and Hofbauer [15] give m. p. 152—153°. [b] Wolfes and Hromatka [16] give m. p. 156—158°. [c] Wolfes and Hromatka [16] give m. p. 225—270°. [d] Found: N, 2·4. $C_{54}H_{70}O_6N_2I_2,2H_2O$ requires N, 2·5%.

Chemistry.—All transesterifications were carried out at 120—140° at water-pump pressure for 6 hr. in xylene containing sodium ethoxide (2% of Na).[1, 15]

M. p.s and analyses of tropine and ψ-tropine benzilates and their derivatives are given in Table 2.

[9] Jowett and Pyman, 7th Internat. Congr. Appl. Chem., 1909, IVA, i, 335.
[10] "The Alkaloids," Ed. Holmes and Manske, Academic Press, New York, 1955, Vol. V, pp. 252—257.
[11] Kimura and Unna, *J. Pharmacol.*, 1950, **98**, 286.
[12] Pulewka, *Arch. exp. Path. Pharmak.*, 1932, **168**, 307.
[13] Ing, Dawes, and Wajda, *J. Pharmacol.*, 1945, **85**, 85.
[14] Ford-Moore and Ing., *J.*, 1947, 55.
[15] Hromakta, Csoklich, and Hofbauer, *Monatsh.*, 1952, **73**, 1321.
[16] Wolfes and Hromakta, *Chem. Zentr.*, 1938, I, 2755.

ψ-Tropine α-benzylmandelate. Ethyl diphenylcyanoacetate [17] (m. p. 59°) was hydrogenated (Raney nickel) in ethanol at room temperature and 6 atm. (60 hr.). After removal of the catalyst and solvent the product was dissolved in dry ether and *ethyl β-amino-αα-diphenylpropionate hydrochloride* precipitated by dry hydrogen chloride (yield, 70%; m. p. 197°). A specimen crystallized twice from ethyl methyl ketone had m. p. 199° (Found: C, 66·6; H, 6·4. $C_{17}H_{19}O_2N$,HCl requires C, 66·8; H, 6·5%). A solution of the crude hydrochloride (45 g.) in 0·5N-sulphuric acid (600 ml.) at 0° was treated dropwise with sodium nitrite (45 g.) in water (100 ml.) with stirring, which was continued without ice-cooling for 3 hr. after the addition of nitrite. Excess of nitrous acid was decomposed by urea, the mixture extracted twice with ether, and the extract washed successively with N-sulphuric acid, aqueous potassium carbonate, and water. The dried extract (Na_2SO_4) gave *ethyl α-benzylmandelate* as a pale yellow oil, b. p. 158°/1 mm. (20 g., 40%) (Found: C, 75·3; H, 6·5. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%). Transesterification of this ester with *ψ*-tropine gave a small yield of acid-soluble oil, which solidified slowly. Two crystallizations from ethyl methyl ketone gave slender needles of *ψ-tropine α-benzylmandelate*, m. p. 135° (Found: C, 75·4; H, 7·4. $C_{23}H_{27}O_3N$ requires C, 75·5; H, 7·4%). The *methiodide*, crystallized from ethanol, had m. p. 224° (decomp.) (Found: C, 56·5; H, 6·2. $C_{24}H_{30}O_3NI$ requires C, 56·7; H, 5·9%).

Tropine phenyl-2-thienylglycollate was obtained by transesterification of tropine with ethyl phenyl-2-thienylglycollate, prepared from the silver salt of the free acid.[18] The acid-soluble product, crystallized from 70% (v/v) aqueous ethanol, had m. p. 151° (yield, 5%) (Found: C, 66·9; H, 6·0. $C_{20}H_{23}O_3NS$ requires C, 67·4; H, 6·4%).

Tropine 9-hydroxyfluorene-9-carboxylate was prepared by transesterification of tropine with ethyl 9-hydroxyfluorene-9-carboxylate; the product (8%), crystallized from 70% (v/v) aqueous ethanol, had m. p. 176° (Found: C, 75·7; H, 6·5. $C_{22}H_{23}O_3N$ requires C, 75·7; H, 6·6%). The *methiodide* was obtained as long needles (from ethanol), decomp. 190° (Found: C, 55·9; H, 5·4. $C_{23}H_{26}O_3NI$ requires C, 56·2; H, 5·3%).

DEPARTMENT OF PHARMACOLOGY, OXFORD. [*Received, April 10th*, 1957.]

[17] Bickel, *Ber.*, 1889, **22**, 1537.
[18] Blicke and Tsao, *J. Amer. Chem. Soc.*, 1944, **66**, 1645.