[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Isosteric Compounds. III.[1] Tertiary Dibenzothienyl Amino Alcohols

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The possibility of isosteric replacement of benzene and benzene derivatives by thiophene and its respective derivatives has been demonstrated beyond doubt by Erlenmeyer and his co-workers.[2] A number of physical properties which depend upon the electronic arrangement of the compounds, and the physiological effects of analogous derivatives are very similar in the two series.

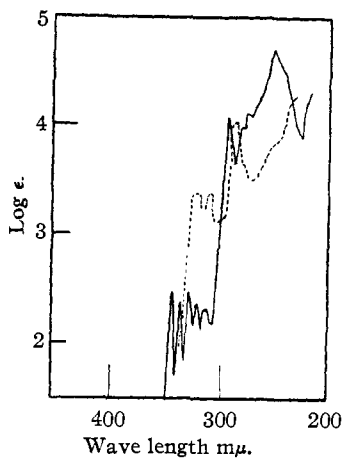


Fig. 1.—Phenanthrene[6] ———; dibenzothiophene[7] - - - - -.

Isosterism was also found in the corresponding derivatives of pyridine and thiazole, but their properties do not match as well as in the benzene and thiophene series.[3] It was of interest to investigate whether isosterism would be observed in compounds containing condensed ring systems in which a benzene nucleus is replaced by a thiophene nucleus. Recently, Sandin and Fieser[4] synthesized an isolog of 9,10-dimethyl-1,2-benzanthracene containing a terminal thiophene nucleus in order to test the carcinogenity of this compound. A comparison of amino alcohols derived from dibenzothiophene and phenanthrene is reported in our present article.

(1) (a) I, Burger, Wartman and Lutz, THIS JOURNAL, **60**, 2628 (1938); (b) II, Burger and Bryant, *J. Org. Chem.*, **4**, 119 (1939).

(2) Erlenmeyer, Berger and Leo, *Helv. Chim. Acta*, **16**, 733 (1933); Erlenmeyer and Leo, *ibid.*, **16**, 1381 (1933).

(3) Erlenmeyer and co-workers, *ibid.*, **20**, 204, 310, 1388 (1937); **21**, 709, 863, 1013, 1017, 1695 (1938); **22**, 698, 938 (1939); **23**, 197, 328, 1268 (1940); Finkelstein and Elderfield, *J. Org. Chem.*, **4**, 365 (1939); Schmelkes, *Science*, **90**, 113 (1939); Schmelkes and Joiner, THIS JOURNAL, **61**, 2562 (1939); Baumgarten and Dornow, *Ber.*, **73**, 353 (1940); Northey, *Chem. Rev.*, **27**, 85 (p. 103) (1940).

(4) Sandin and Fieser, THIS JOURNAL, **62**, 3098 (1940).

It was realized that such a comparison would suffer from the fact that the "aromatic" sulfur[5] atom in dibenzothiophene is supposed to replace the 9,10-ethene group in phenanthrene, and that the latter occupies an intermediate position between carbon atoms linked by a resonating aromatic and an olefinic double bond. An inspection of the ultraviolet absorption spectra of phenanthrene[6] and dibenzothiophene[7] (Fig. 1) showed that the two compounds do not agree in this important physical property. Moreover, phenanthrene and dibenzothiophene do not form mixed crystals; this was determined by studying the melting point diagram of mixtures of the two compounds by the method of Rheinboldt[8a] (Fig. 2). Although Grimm[8b] found that isomorphism is not a strict criterion for isosterism, the variance of two important physical characteristics may indicate absence of isosterism in our case. This may be due not only to the peculiar character of the 9,10-ethene bridge in phenanthrene, but also perhaps to a distortion of the thiophene nucleus in dibenzothiophene. Both

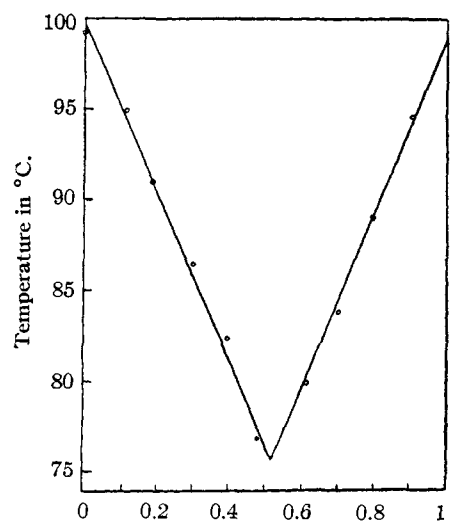


Fig. 2.—Melting points of mixtures of phenanthrene and dibenzothiophene.

(5) Schomaker and Pauling, *ibid.*, **61**, 1769 (1939).

(6) Clar, *Ber.*, **65**, 846 (1932).

(7) Chaix, *Bull. soc. chim.*, **53**, 700 (1933).

(8) (a) Rheinboldt, *J. prakt. Chem.*, **111**, 242 (1925); **112**, 187 (1926); **113**, 199, 348 (1926); (b) Grimm, Günther and Tittus, *Z. physik. Chem.*, **B14**, 169 (1931).

α- and both β-positions are condensed with aromatic nuclei, and the distance between the atoms of the heterocyclic ring cannot be the same as in an uncondensed thiophene nucleus. The possibility of a similiar distortion was pointed out by Hinsberg[9] for thiophene derivatives in which only the β-positions of the heterocyclic nucleus are condensed.

Dibenzothiophene and a number of its derivatives were tested for possible analgesic effects by Dr. Nathan B. Eddy of the U. S. Public Health Service, Washington, D. C. He found that dibenzothiophene, like phenanthrene, dibenzofuran and carbazole, is a relatively inert substance when administered orally to cats. It is very slightly depressant but less so than phenanthrene. 2-Acetyldibenzothiophene exhibits a greater quieting effect but is less depressant than 3-acetylphenanthrene or 2-acetyldibenzofuran.

In testing four amino alcohols derived from dibenzothiophene (substances 6, 10, 20, and 25), Dr. Eddy found a similar picture in mice in toxic doses, depression with marked disturbance of coördination. The order of toxicity was 2-(2-diethylamino - 1 - hydroxyethyl) - dibenzothiophene (least), 2-(3-dimethylamino-1-hydroxypropyl)-, 2-(2-piperidino-1-hydroxyethyl)-, and 2-(3-piperidino - 1 - hydroxypropyl)-dibenzothiophene (most toxic). Administered orally to cats all four exhibited analgesic action, effective doses ranging from 30 to 75 mg. per kg. The order of effectiveness was not the same as the order of toxicity. The compounds had little quieting effect; on the other hand, with doses not greatly above those which caused analgesia, reflexes were sometimes increased and convulsions occurred in some cases. As far as comparisons are available the analgesic effectiveness of these compounds is of the same order as with compounds derived by the introduction of similar substituents into the dibenzofuran, carbazole and phenanthrene nuclei.[10]

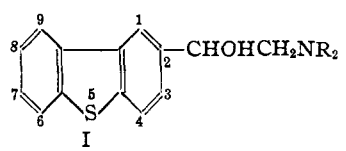
It seems inadvisable to use the similar pharmacological behavior of the corresponding phenanthrene and dibenzothiophene derivatives as a support for isosterism of these two series, since the analogous derivatives of other tricyclic systems do not show a more pronounced difference, although such a difference should be expected on the basis of the theory of isosterism.

(9) Hinsberg, *Ber.*, **43**, 901 (1910).

(10) *Cf.* also Burtner and Lehmann, THIS JOURNAL, **62**, 527 (1940).

Dibenzothiophene amino alcohols were prepared by the general methods outlined for similar cases in previous communications from this Laboratory. The yield in the preparation of dibenzothienyl-α-tertiary amino ketones from 2-bromoacetyldibenzothiophene and secondary amines varied greatly depending on the amine employed in the reaction. Piperidine and 1,2,3,4-tetrahydroisoquinoline gave the best results, diethylamine gave yields inferior to dimethylamine, and di-cyclohexylamine could not be induced to react with the bromo ketone. The exchange of the α-bromine atom with the diethylamino group seemed to be a side reaction, since the reaction products consisted mainly of a mixture of non-basic materials from which several substances of undetermined structure could be separated by fractional crystallization.

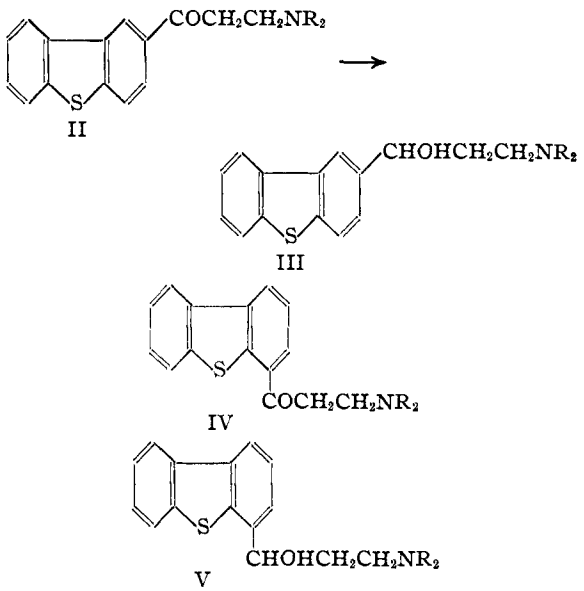
Catalytic reduction of salts of the tertiary 2-dibenzothienyl-α-amino ketones yielded salts of the corresponding α-amino alcohols (I). The reaction was completed in most cases when one mole of hydrogen was absorbed.



I

Tertiary dibenzothienyl-β-amino ketones (II and IV) were obtained from 2- and 4-acetyldibenzothiophene and the hydrochlorides of secondary amines by the Mannich reaction; the condensation was carried out advantageously in boiling isoamyl alcohol. Dicyclohexylamine was again too inert to enter into this condensation. The reaction with diethylamine yielded mainly a non-basic product, but the formation of this compound could be avoided by using cyclohexanol as a solvent.

Catalytic hydrogenation of the β-amino ketone hydrochlorides furnished the corresponding dibenzothienyl-β-amino alcohols (III and V). Absorption of hydrogen usually did not exceed the calculated amount, but hydramine fission accompanied the reduction much more noticeably than in the α-series. Varying amounts of 2-propionyldibenzothiophene were isolated from the non-basic fractions in the reduction of different 2-dibenzothienyl-β-amino ketones. Careful purification of these starting materials resulted in an increased rate of hydrogenation and a suppression of the slower hydramine fission.



Experimental

General Procedures

2-Dibenzothienyl-α-amino Ketones.—2-ω-Bromoacetyldibenzothiophene[1b] was allowed to react with two moles of the respective secondary amine in an inert solvent, usually benzene, at temperatures and over periods of time specified in the footnotes to the table. The amine hydrobromide formed in the reaction was extracted into water, and the amino ketone, obtained by evaporation of the dried benzene solution, was converted into the hydrochloride in acetone solution.

The exchange of the bromine atom with the 1,2,3,4-tetrahydroisoquinolino group gave the best results in dioxane solution. The reaction mixture was worked up according to footnote *i* of Table I.

2-Dibenzothienyl-α-amino Alcohols (I).—The carefully purified halides of the α-amino ketones were hydrogenated in methanol solution in the presence of a platinum oxide catalyst. Hydrogen absorption was completed after eight to fifty hours depending on the nature of the compound. The catalyst was filtered, the solvent evaporated under re-

TABLE I

	Derivatives of dibenzothiophene[w]	Solvent	Yield, %	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	2-(2-Dimethylamino-1-oxoethyl)-HCl[c]	MeOH–Et2O	54	220–225[a]	$C_{16}H_{16}ClNOS$					4.58	4.94
2	-1-hydroxyethyl)-HCl	MeOH–Et2O	50	228–228.5[a]	$C_{16}H_{18}ClNOS$	62.42	62.20	5.89	5.85	4.55	4.53
3	-1-acetoxyethyl)-HCl[b]	Me2CO–Et2O		206–208[a]	$C_{18}H_{20}ClNO_2S$					4.00	4.35
4	2-(2-Diethylamino-1-oxoethyl)-HCl[d]	EtOH–Et2O	55	214–215[a,e]	$C_{18}H_{20}ClNOS$					See ref. 1b	
5	-1-hydroxyethyl)-[x]	Me2CO–H2O		59–60	$C_{18}H_{21}NOS$					4.68	4.39
6	-Hydrochloride	EtOH–Et2O	69	163–164	$C_{18}H_{22}ClNOS$	64.36	64.01	6.60	6.52	4.17	4.58
7	-1-acetoxyethyl)-HCl[b]	EtOH–Et2O		188–192[a]	$C_{20}H_{24}ClNO_2S$	63.56	62.99	6.40	6.58	3.71	3.54
8	2-(2-Piperidino-1-oxoethyl)-[f]	Me2CO–H2O		117	$C_{19}H_{19}NOS$					4.53	4.39
9	-1-hydroxyethyl)-	Me2CO–H2O		88–89	$C_{19}H_{21}NOS$					4.50	4.37
10	-Hydrochloride	MeOH–Et2O	86	225–229[a]	$C_{19}H_{22}ClNOS$	65.59	65.24	6.37	6.31	4.03	4.08
11	-1-acetoxyethyl)-HCl[b]	EtOH–Et2O		220–225[a]	$C_{21}H_{24}ClNO_2S$					3.59	3.59
12	2-[2-(1,2,3,4-tetrahydroisoquinolino)-1-oxoethyl]-[g,z]	Me2CO		122–125	$C_{28}H_{19}NOS$						
13	-Hydrochloride[h]	MeOH		244–246[a]	$C_{28}H_{20}ClNOS$					3.56	3.77
14	-Hydrobromide[i]	MeOH	59	257–259[a]	$C_{28}H_{20}BrNOS$					3.20	3.45
15	2-[2-(1,2,3,4-tetrahydroisoquinolino)-1-hydroxyethyl]-[j]	Me2CO–H2O		106–107	$C_{28}H_{21}NOS$	76.84	76.82	5.89	5.97	3.90	3.99
16	-Hydrochloride[k]	MeOH–Et2O		243–244[a]	$C_{28}H_{22}ClNOS$					3.54	3.24
17	-Hydrobromide[l]	MeOH–Et2O	80	250–252[a]	$C_{28}H_{22}BrNOS$					3.18	3.53
18	2-(3-Dimethylamino-1-oxopropyl)-HCl[m]	MeOH–Et2O	41[n]	192–195[a]	$C_{17}H_{18}ClNOS$					4.38	4.05
19	-1-hydroxypropyl)-[o]	Me2CO–H2O		118	$C_{17}H_{19}NOS$					4.91	5.18
20	-Hydrochloride[z]	EtOH–Et2O	64	137–139	$C_{17}H_{20}ClNOS$	63.44	63.14	6.26	6.34	4.35	4.51
21	-1-acetoxypropyl)-HCl[b]	EtOH–Et2O		149–150	$C_{19}H_{22}ClNO_2S$	62.71	62.49	6.10	6.01	3.85	4.17
22	2-(3-Diethylamino-1-oxopropyl)-HCl[p]	EtOH	40	150–151	$C_{19}H_{22}ClNOS$					4.03	4.30
23	2-(3-Piperidino-1-oxopropyl)-HCl[q]	EtOH–Et2O	55	201–203[a]	$C_{20}H_{22}ClNOS$					3.89	4.26
24	-1-hydroxypropyl)-[o]	Me2CO–H2O		102	$C_{20}H_{23}NOS$					4.30	4.14
25	-Hydrochloride	EtOH–Et2O	59	201–201.5[a]	$C_{20}H_{24}ClNOS$	66.37	66.30	6.68	6.45	3.87	3.71
26	-1-acetoxypropyl)-HCl[b]	EtOH–Et2O		185–186	$C_{22}H_{26}ClNO_2S$					3.47	3.81
27	2-[3-(1,2,3,4-tetrahydroisoquinolino)-1-oxopropyl]-[o]	Me2CO–H2O		106–107	$C_{24}H_{21}NOS$					3.77	3.70
28	-Hydrochloride[m]	MeOH	30[n]	197–198[a]	$C_{24}H_{22}ClNOS$					3.43	3.72
29	2-[3-(1,2,3,4-tetrahydroisoquinolino)-1-hydroxypropyl]-[o]	Me2CO–H2O		136	$C_{24}H_{23}NOS$	77.17	76.71	6.21	6.23	3.75	3.85
30	-Hydrochloride	MeOH	46	183–185[a]	$C_{24}H_{24}ClNOS$					3.42	3.37
31	2-[3-(1,2,3,4-tetrahydroisoquinolino)-1-acetoxy-propyl]-HCl[b]	Me2CO–Et2O		193–196[a]	$C_{26}H_{26}ClNO_2S$					3.10	3.33
32	4-(3-Piperidino-1-oxopropyl)-[o]	Me2CO–H2O		112	$C_{20}H_{21}NOS$					4.33	4.16
33	-Hydrochloride[r,z]	MeOH–Et2O	40	229–232[a]	$C_{20}H_{22}ClNOS$	66.74	66.85	6.16	6.03	3.89	4.33
34	4-(3-Piperidino-1-hydroxypropyl)-[s,z]	EtOH–H2O	50	105	$C_{20}H_{23}NOS$	73.78	73.59	7.12	7.18	4.30	4.45
35	2-Propionyl-[t,z]	EtOH		72–72.5	$C_{15}H_{12}OS$	74.97	74.85	5.03	5.05		
36	-Semicarbazone[u,z]	EtOH–H2O		196–198	$C_{16}H_{15}N_3OS$					14.13	14.48
37	2-(1-Hydroxyethyl)-	Petroleum ether	68	76–77	$C_{14}H_{12}OS$	73.65	73.77	5.30	5.56		
38	2-(1-Acetoxyethyl)-[v,y]				$C_{16}H_{14}O_2S$	71.08	70.82	5.22	5.55		

[a] M. p. (dec., evacuated tube). [b] From the amino alcohol hydrochloride with acetic anhydride in pyridine solution. The oily acetoxy derivative was converted to the hydrochloride in acetone–ether solution. [c] Prepared in benzene solution, heating at 100° for 22 hours, and working up the mixture according to the general procedure. [d] Prepared according to the general directions in benzene solution, three hours at 27°. A colorless by-product containing no nitrogen was isolated from the mother liquors by repeated crystallization from acetone; m. p. 263–266° (dec., evacuated tube). [e] Previously reported,[1b] 200–202° (dec.). [f] From the hydrochloride[1b] with ammonium hydroxide. [g] From no. 14 with dilute ammonium hydroxide. The compound decomposed on recrystallization and was not analyzed. [h] From no. 12 with hydrogen chloride in dioxane–ether solution. [i] Prepared in dioxane solution, two hours at room temperature. The hydrobromide crystallized from the reaction mixture and was washed with water to remove tetrahydroisoquinoline hydrobromide. The dioxane mother liquors contained some tetrahydroisoquinolino ketone (no. 12) which was precipitated as the hydrochloride (no. 13) by addition of ethereal hydrogen chloride. [j] From the hydrobromide (no. 17) with ammonium hydroxide. [k] From no. 15 with hydrogen chloride in acetone–ether solution. [l] From no. 14 by hydrogenation according to the general directions. [m] Prepared in boiling isoamyl alcohol solution; reaction time, twenty minutes. [n] Based on the amount of 2-acetyldibenzothiophene which had entered into the reaction. [o] From the hydrochloride with ammonium hydroxide. [p] Prepared by boiling in cyclohexanol solution for one hour. If isoamyl alcohol was used, a non-basic compound was the main reaction product. It crystallized from ethanol as colorless needles, m. p. 82–82.5°. The β-diethylamino ketone hydrochloride absorbed an excess of 10–50% of hydrogen, but neither the diethylamino alcohol nor any derivative could be crystallized. 2-Propionyldibenzothiophene was isolated in the usual manner. [q] Prepared by boiling in isoamyl alcohol solution for seven minutes. [r] Prepared in boiling isoamyl alcohol; reaction time, one hour. [s] Prepared from no. 33 by catalytic hydrogenation. The reaction mixture was evaporated, the residue dissolved in water, extracted with ether, the aqueous solution was made alkaline, and the piperidino alcohol was filtered. [t] Obtained by hydramine fission from all the hydrogenations of the β-amino ketone hydrochlorides. [u] From no. 35 with semicarbazide acetate in dilute ethanol. [v] From the carbinol (no. 37) with acetic anhydride in pyridine solution at room temperature. Purified by distillation at 80° under 0.1 mm. pressure. [w] All compds. are colorless. They formed needles (unless stated otherwise in footnotes *x* and *y*) on crystallization. [x] Plates. [y] Colorless oil.

duced pressure, the residue was treated with acetone, and the amino alcohol halides were filtered and recrystallized.

2- and 4-Dibenzothienyl-β-amino Ketones (II, IV).—One mole of acetyldibenzothiophene, one and one-tenth moles of the secondary amine hydrochloride, and three moles of paraformaldehyde were refluxed in isoamyl alcohol or cyclohexanol solution over different periods of time depending on the amine used. The β-amino ketone hydrochlorides either crystallized on cooling, or were precipitated by addition of ether to the cooled reaction mixture.

2- and 4-Dibenzothienyl-β-amino Alcohols (III, V).—The hydrochlorides of the β-amino ketones (II, IV) were dissolved in an adequate amount of methanol, and hydrogenated in the presence of a platinum oxide catalyst. Hydrogenation was completed after four to twenty-five hours, a slight excess of hydrogen being absorbed in most cases. After filtration from the catalyst, the solvent was removed under reduced pressure, and the residue usually crystallized on treatment with acetone.

The mother liquors of the 2-dibenzothienyl-β-amino alcohol hydrochlorides were concentrated, diluted with ether, and extracted with dilute acid. Hydramine scission always accompanied the reduction, and 2-propionyldibenzothiophene was isolated from the ether solution by evaporation and recrystallization.

2-(1-Hydroxyethyl)-dibenzothiophene.—A solution of 2.5 g. of 2-acetyldibenzothiophene in 50 ml. of dry isopropyl alcohol was added to a solution of aluminum isopropylate prepared from 2.5 g. of aluminum turnings according to the directions of Bachmann and Edgerton.[11] The mixture was boiled under reflux for three hours, cooled, decomposed by gradual addition of 50 ml. of 5% sulfuric acid, and extracted with benzene. The residue from the benzene extract crystallized from petroleum ether.

Summary

A number of α- and β-tertiary amino alcohols derived from dibenzothiophene was synthesized. The analgesic effect of several of these compounds, and the physiological action of dibenzothiophene and 2-acetyldibenzothiophene, was tested.

Dibenzothiophene and phenanthrene do not agree in their absorption spectra and do not exhibit isomorphism. Although the pharmacological properties of the corresponding derivatives of phenanthrene and dibenzothiophene are similar, they do not support the assumption that the two series are isosteric.

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(11) Bachmann and Edgerton, THIS JOURNAL, **62**, 2970 (1940).