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On the Action of the Optical Isomers of Adrianol, Corbasil, Sympatol and Ephedrine on Isolated Intestine.

By

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The biological relations of optically isomeric substances have been reviewed by CUSHNY (1926). With regard to adrenaline and its substitutes the pharmacodynamical properties of the optical isomers have been the subject of a great deal of research. AHLGREN (1929) found l-adrenaline more than 10 times as active as the d-isomer on isolated intestine; LINDNER and GÖPFERT (1938) report that the isomers of veritol have identical action. The literature dealing with the investigated drugs will be considered below.

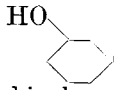
Methods.

All the experiments were performed on isolated surviving rabbit's small intestine according to the Magnus technique. The rabbits were killed by a blow on the occiput followed by bleeding from the carotid artery. The intestinal segments were suspended in Tyrode solution at a temp. of 38° C. Through the solution, which consisted of NaCl 0.8 %, KCl 0.02 %, $CaCl_2$ 0.01 %, $MgCl_2$ 0.01 %, Na_2HPO_4 0.005 % and $NaHCO_3$ 0.01 %, was bubbled a mixture of 95 % O_2 and 5 % CO_2.

The following drugs were used: l-adrenaline-hydrochloride, l-corbasil-hydrochloride, d-corbasil base, d-, l- and dl-ephedrine-hydrochloride from I. G. Farbenindustrie and l-adrianol-hydrochloride, d-adrianol-tartrate, d- and l-sympatol-hydrochloride from C. H. Boeh-

ringer Sohn.[1] The concentrations of the drugs are calculated as γ/m free base. In preparing the solutions of d-corbasil the calculated quantity of n/10 hydrochloric acid was added.

Adrianol.



$CH(OH)CH_2NHCH_3$, methylaminomethyl(3-oxyphenyl) carbinol.

In Anglo-american literature generally called meta-synephrine or neosynephrine (the l-isomer), in German literature known as adrianol.

The pharmacological properties of adrianol were first investigated by KUSCHINSKY and OBERDISSE (1931). They found the inhibiting action of dl-adrianol on isolated intestine to be about 1/12 of that of adrenaline. BOYD (1937) found l-adrianol about $^1/_2$ as active as l-adrenaline on isolated intestine, while AUMANN and YOUMANS (1939) report the corresponding figure to be 1/4—1/10.

Some information on the action of l- and d-adrianol on isolated intestine may be gained from the tracings in the paper of DRAKE, JOHN, RENSHAW and THIENES (1939) on the responses of denervated smooth muscle to adrenaline substitutes. l-Adrianol seems to inhibit the intestine in conc. 0.5—1.0 γ/ml, d-adrianol in conc. 2.0—10.0 γ/ml.

TAINTER and STOCKTON (1939) compared the circulatory action of the optical isomers of adrianol and found the l-form about 40 times as active as the d-isomer. They were also able to establish a qualitative difference in the action of the isomers, as cocaine potentiated the action of l-adrianol but not of d-adrianol.

Own investigations: In conc. less than 0.2 γ/ml l-adrianol does not affect the isolated intestine. Conc. 0.3—0.8 γ/ml markedly decrease tone and amplitude and often cause temporary complete paralysis of pendulum movements. The effect is qualitatively quite similar to that of adrenaline; the activity of l-adrianol is about 1/10 of that of l-adrenaline.

d-Adrianol was found to be inactive in conc. less than 0.5 γ/ml. Conc. 0.5—2.0 γ/ml in most cases stimulated the intestine (increase of tone and amplitude); in some cases no effect could be demonstrated. However, this stimulant effect of d-adrianol is rather weak and inconstant. In conc. higher than 50 γ/ml d-adrianol depresses the gut. 50—200 γ/ml give a very weak and tran-

[1] I am most indebted to I. G. Farbenindustrie AG., Leverkusen am Rh. for a supply of the isomers of corbasil and ephedrine and to C. H. Boehringer Sohn, Ingelheim am Rh. for the isomers of adrianol and sympatol.

sitory effect; 300—700 γ/ml give an inhibitory effect of moderate strength (slight fall of tone, decrease of amplitude to about $^1/_2$). Thus the inhibiting activity of d-adrianol is about 1/10000 of l-adrianol and 1/100000 of l-adrenaline although the effects are qualitatively quite similar.

It will be noticed that d-adrianol stimulates the intestine in the same conc. at which l-adrianol has a very strong inhibiting effect. (See fig. 1.)

Obviously there is a considerable discrepancy between the findings of DRAKE, JOHN, RENSHAW and THIENES (loc. cit.) and mine as to the action of d-adrianol. A possible explanation of this difference is that the former investigators have used a preparation of d-adrianol containing some l-adrianol.

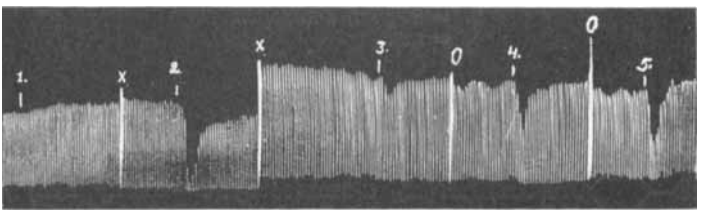


Fig. 1. Isolated rabbit's intestine in Tyrode solution.

1. = 0.8 γ/ml d-adrianol.
2. = 0.8 γ/ml l-adrianol.
3. = 70 γ/ml d-adrianol.
4. = 220 γ/ml d-adrianol.
5. = 360 γ/ml d-adrianol.
× = washing.
0. = washing 3 times.

MODERN and THIENES (1936) have investigated the antagonism towards adrenaline of a series of adrenaline substitutes. They found that neither l- nor d-adrianol exhibited any ability to antagonize the inhibiting action of adrenaline on isolated intestine. An accidental observation during an experience with d- and l-adrianol made me reinvestigate this problem. It was possible to demonstrate that d-adrianol in conc., which do not affect the intestinal motility in any way (20—40 γ/ml), greatly diminishes or completely abolishes the inhibiting action of l-adrianol (0.5—0.8 γ/ml) or l-adrenaline (0.05—0.08 γ/ml) (See fig. 2.), whereas — curiously enough — the inhibiting action of l-corbasil (0.10—0.30 γ/ml) is *not* decreased. After repeated washing with fresh Tyrode solution the effects of l-adrianol and l-adrenaline appear

again with full strength. In most cases, however, the primary inhibiting effect is followed by a secondary stimulation of the intestine. Generally this phenomenon is very often noticed following the influence of sympathicolytic drugs on the intestine and must be considered to have some connection with the supposed blockade of the sympathetic receptors.

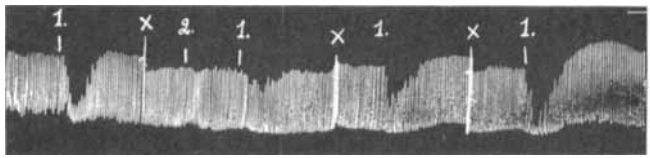
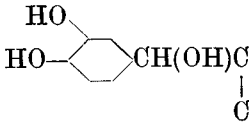


Fig. 2. Isolated rabbit's intestine in Tyrode solution.
1. = 0.8 γ/ml l-adrianol.
2. = 30 γ/ml d-adrianol.
× = washing.

Corbasil.



α-aminoethyl(3—4dioxyphenyl)carbinol, 3—4dioxynorephedrine, cobefrine.

In his fundamental pharmacological investigation of oxy-ephedrines SCHAUMANN (1931) found that corbasil inhibits the isolated intestine and that the inhibiting activity of dl-corbasil is about $^1/_2$ of that of 1-adrenaline. CHEN and LING CHEN (1933) and HOYT, PATEK and THIENES (1934) confirm that corbasil inhibits the intestine without giving any detailed information on the effect. AUMANN and YOUMANS (loc. cit.) found dl-corbasil $^1/_3$—$^1/_5$ as active as 1-adrenaline.

SCHAUMANN (1936) has investigated the action of the optical isomers of corbasil on blood pressure and uterus. According to him the l-form is 160—250 times as active as the d-isomer on blood pressure and 1 200 times as active on uterus. SCHAUMANN also found the effects qualitatively dissimilar. The circulatory effect of l-corbasil is similar to that of adrenaline, while the effect of d-corbasil corresponds to that of ephedrine. Cocaine potentiates the action of l-corbasil but diminishes that of d-corbasil.

Own investigations: In conc. less than 0.01 γ/ml l-corbasil has no influence on intestinal motility. Conc. 0.10—0.30 γ/ml regularly inhibit the intestine (fall of tone, paralysis of pendulum movements). The effect is qualitatively quite similar to that of adrenaline; the activity of l-corbasil is $^1/_2$—$^1/_3$ of l-adrenaline.

d-Corbasil is inactive in conc. less than 0.20 γ/ml. In most cases it stimulates the intestine (moderate increase of amplitude or tone or both) in conc. 0.30—0.60 γ/ml. However, this stimulant effect is rather weak and cannot always be reproduced. In conc. higher than 10 γ/ml d-corbasil depresses the intestine. The inhibiting effect is qualitatively identical with that of l-corbasil, but the l-isomer is about 200 times as active.

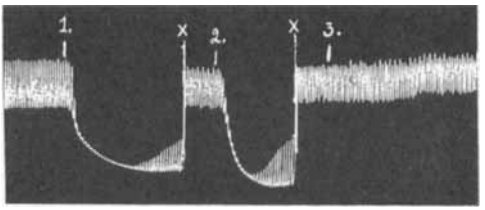


Fig. 3. Isolated rabbit's intestine in Tyrode solution.

1. = 0.20 γ/ml l-corbasil.
2. = 40 γ/ml d-corbasil.
3. = 0.36 γ/ml d-corbasil.
× = washing.

Just as is the case with the isomers of adrianol d-corbasil stimulates the intestine in the same conc., at which l-corbasil has a very strong inhibiting action.

MODERN and THIENES (loc. cit.) report that dl-corbasil does not antagonize adrenaline on isolated intestine. In accordance with this it was found that d-corbasil — contrary to d-adrianol — in conc. up to 20 γ/ml does not diminish the response to l-adrenaline, l-adrianol or l-corbasil.

Sympatol.

HO⟨⟩$CH(OH)CH_2NHCH_3$, methylaminomethyl(4-oxyphenyl) carbinol.

In Anglo-american literature known as synephrine or para-synephrine.

LASCH (1927) and EHRISMANN and MALOFF (1928) report that sympatol inhibits the isolated rabbit's and rat's small intestine in conc. 100—500 γ/ml. KUSCHINSKY (1930) finds the inhibiting activity of sympatol to be about 1/100 of adrenaline; he regards the effects of adrenaline and sympatol as qualitatively identical. AUMANN and YOUMANS (loc. cit.) report that l-adrenaline is 500—1 000 times as active as dl-sympatol on isolated intestine. TAINTER and SEIDENFELD (1930) find the effects of sympatol on isolated rabbit's intestine very weak and inconstant. According to them l-sympatol inhibits the intestine in conc. 60—1 000 γ/ml. d-Sympatol stimulates it in conc. about 200 γ/ml (increase of tone but not of amplitude) but has an inhibiting effect in higher conc. The authors consider the inhibiting effect as due not to sympathetic stimulation but to direct muscular depression.

KUSCHINSKY (loc. cit.) finds l-sympatol more than 50 times as active as the d-isomer on blood pressure.

Own investigations: On the whole I was able to confirm the findings of Tainter and Seidenfeld. l-Sympatol is inactive in conc. less than 10 γ/ml. In conc. 25—1200 γ/ml l-sympatol inhibits the intestine (decrease of tone or amplitude or both). The highest conc. often cause complete paralysis of pendulum movements. In these cases the effect may be rather difficult to wash out, 3—4 washings with fresh Tyrode solution being necessary for complete restoration of the motility of the intestine. It may be added that l-sympatol was never seen to stimulate the intestine.

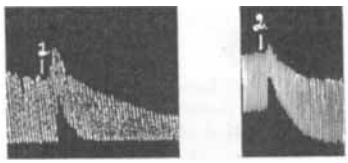


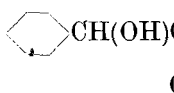
Fig. 4. Isolated rabbit's intestine in Tyrode solution.
1. = 220 /ml l-sympatol.
2. = 160 /ml l-sympatol.
Note the "motorial peak", which is unusually well developed.

In some cases a weak and transitory increase of intestinal tone ("motorial peak") was seen immediately following the introduction of the drug. (See fig. 4.) This increase of tone is always accompanied by a decrease of amplitude.

In most cases d-sympatol stimulates the intestine in conc. 110—200 γ/ml (increase of tone or amplitude or both) but this stimulant effect is rather weak and cannot always be reproduced. In conc. 250—1200 γ/ml d-sympatol inhibits the intestine. The effect is qualitatively identical with that of l-sympatol; the activity is about $^1/_2$ of the l-isomer.

The inhibiting effect of l- as well as of d-sympatol may be reproduced again and again, and the reactivity of the intestine does not seem to diminish in the course of the experiment. It may be emphasized that the inhibiting effect of sympatol is qualitatively quite different from that of adrenaline as it is never momentary but develops gradually and slowly; in many cases it is rather difficult to wash out.

Ephedrine.



$CH(OH)CHNHCH_3$, α-methylaminoethylphenylcarbinol.
CH_3

The very extensive literature on the action of ephedrine on isolated intestine is reviewed by CHEN and SCHMIDT (1930). Later KINOSHITA (1930—31) and NUKITA (1935) report that ephedrine always inhibits

the intestine. TERADA (1939) finds that low conc. are without effect or slightly depressant, whereas higher conc. have an inhibiting effect. Unfortunately these reports are too brief to evaluate. WEBER (1939) reports that ephedrine in most cases stimulates the isolates rabbit's intestine in conc. 0.04—0.4 γ/ml. THIENES (1934) and PATEK and THIENES (1935) find that l-ephedrine occasionally augments the isolated rabbit's intestine in conc. 10—50 γ/ml but in most cases inhibits it (conc. 10—200 γ/ml.). dl-Ephedrine is in most cases inactive (2—160 γ/ml), in one case inhibition was found in conc. 10 γ/ml. The authors conclude that dl-ephedrine has much weaker muscle contracting properties than l-ephedrine. CHEN, WU and HENRIKSEN (1929) report only inhibition of the intestine (15—40 γ/ml); they find l-, d- and dl-ephedrine equally potent.

Obviously the opinions as to the action of ephedrine on isolated intestine are very much divergent, some workers finding that ephedrine is only depressant, others reporting depression and stimulation, still others observing only stimulation. CHEN and SCHMIDT (loc. cit.) explain the discrepancies by assuming that the intestinal effects of ephedrine consist in a combined stimulation of ganglia (plexus of Auerbach), which causes increased motility, and of inhibitory sympathetic nerve endings. KINOSHITA (loc. cit.) concludes that ephedrine acts mainly on the sympathetic nerve endings, whereas the highest doses depress the muscle.

KREITMAR (1927) reported that l- and dl-ephedrine are equally active on blood pressure. Later workers have failed to confirm this. CURTIS (1928) and SCHAUMANN (1928) found the ratio between the activities of dl- and l-ephedrine to be about 1 : 2. PAK and READ (1928) give a ratio of 1 : 1.43, whereas CHEN (1928) finds 1 : 1.33, SCHAUMANN (loc. cit.) finds l-ephedrine 4—5 times as active as d-ephedrine on blood pressure and uterus, while CHEN and HENRIKSEN (loc. cit.) report the ratio 2.95 : 1 on blood pressure.

Own investigations: The optical isomers were found to have an identical action on isolated intestine. Therefore, in the following they are all comprised as ephedrine.

In most cases ephedrine was inactive in conc. 0.005—2.0 γ/ml; occasionally a very weak motorial effect was observed at conc. 0.05—0.05 γ/ml. Very often the intestine was augmented (slight increase of tone but only in a few cases of amplitude) in conc. about 2.5 γ/ml. However, this effect always was very weak and often impossible to reproduce.

Occasionally ephedrine in conc. 4—8 γ/ml has a very weak inhibiting effect. If the conc. is increased to 40—80 γ/ml ephedrine *always* exerts a weak or moderate inhibiting action, which consists in decrease of tone or of amplitude but only in a few cases of both. The effect is never momentary but develops gradually

and slowly just as the effect of sympatol. It is rather easy to wash out and may be reproduced again and again. It will be especially noticed that contrary to a great many statements in the literature ephedrine was found *always* to depress the intestine in conc. higher than 40 γ/ml.

In conc. 110—1100 γ/ml ephedrine always has a very strong inhibiting action on the intestine, consisting in decrease of tone and considerable diminution of amplitude or in many cases complete paralysis of pendulum movements. The repeated reproduction of the effect is perfectly feasible. In many cases it is rather difficult to wash out, 3—4 washings being necessary. In rare cases it may be impossible to restore the motility of the intestine completely. The effect is qualitatively similar to that of sympatol (see fig. 5) and shows the same peculiarities ("motorial peak") as this.

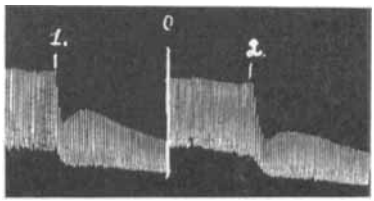


Fig. 5. Isolated rabbit's intestine in Tyrode solution.
1. = 560 γ/ml l-ephedrine.
2. = 560 γ/ml d-ephedrine.
× = washing 3 times.

Discussion.

A quantitative difference is found between the inhibiting activity on isolated intestine of the optical isomers of adrianol, corbasil and sympatol; as generally is the case the l-isomers possess the greatest pharmacodynamical activity. Contrary to this the isomers of ephedrine are equally active. The ratios between the activities of the isomers on isolated intestine are not the same as on blood pressure. Therefore, one is forced to conclude that the isomers of the four investigated drugs also show *qualitative* differences in their pharmacodynamical action, for only if that holds true, it may be expected that the order of potency for a mixed response, such as blood pressure changes, will not be consistent with a single effector response, such as changes in intestinal motility. This conclusion is supported by the finding that the d-isomers of adrianol, corbasil and sympatol in small doses stimulate the intestine, whereas stimulation was never observed upon the introduction of subactive doses of the l-isomers. As it is generally

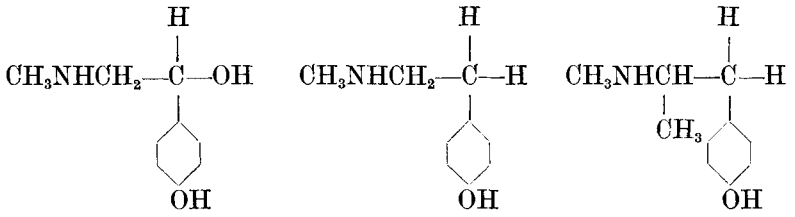
assumed that the intestinal effects of l-corbasil and l-adrianol are similar to or identical with that of l-adrenaline, there is a certain discrepancy between my results and the observation of HOSKINS (1911—12), TASHIRO (1921) and MORIN (1940) that l-adrenaline stimulates the intestine in minimal conc. Perhaps it may be possible by means of some special technique to demonstrate stimulation of the intestine by l-adrianol or l-corbasil. But even in that case the fact remains that the stimulating activity of the d-isomers is of a far greater order of magnitude than that of the l-isomers and therefore the qualitative differences in the mode of action are satisfactorily established.

Several hypotheses have been put forward to explain the different biological reactions of optical isomers (PASTEUR 1886, ERLENMEYER 1919, GOTTLIEB 1923, CUSHNY 1926). However, none of these theories is of any help in explaining qualitative differences in the action of enantiomorphic compounds. This difficulty may be overcome by the aid of the recent theory of EASSON and STEDMAN (1933). These authors conclude that there is no reason for differentiating between molecular dissymmetry and structure in regard to the manner in which they influence physiological activity and on the basis of this qualitative differences in pharmacodynamical action may be understood.

According to the theory of EASSON and STEDMAN the alcoholic hydroxylgroup of the d-isomers of adrenaline and adrenaline substitutes cannot get into close attachment with its specific receptor and therefore the physiological action of the d-isomer will be the same as of a compound lacking the alcoholic hydroxylgroup. Generally the loss of this group in sympathomimetic amines increases the stimulating activity and decreases the inhibiting activity on isolated intestine. Thus, it will be expected that the d-isomers will posses greater stimulating and less inhibiting activity than the l-isomers and this holds true for adrianol, corbasil and sympatol.

A more direct confirmation of the theory may be gained by comparing the action of a d-isomer with that of the corresponding compound lacking the alcoholic hydroxyl-group. Thus, according to EASSON and STEDMAN the action of d-sympatol (I.) should be identical with that of a compound II. The only difference between the compound II. and veritol (III.) is the presence in veritol of a methyl-group in β-position, and it may be presumed that this difference has no significant influence on the activity on isolated

intestine. Indeed a remarkably close agreement was observed between the effects on isolated intestine of d-sympatol and dl-veritol.



I. II. III.

It remains to explain, why an inactivation of the alcoholic hydroxylgroup is followed by very different changes in the inhibiting activity. Thus, the activity of adrianol is diminished to 1/10000, of adrenaline to 1/10, of corbasil to 1/200 and of sympatol to 1/2, while the activity of ephedrine remains unchanged. The difference between adrenaline and adrianol seems to be particularly peculiar, as these drugs qualitatively have the same action.

A new theory has been developed (ORZECHOWSKI, GRONEMEYER and MALORNY 1940, MALORNY and ORZECHOWSKI 1940) to explain the antagonism between sympathomimetica and sympathicolytica. According to this both groups attack the sympathetic receptors. The drugs, which antagonize adrenaline, are characterized by having great "Haftfähigkeit" to, but only inconsiderable stimulating power on the sympathetic receptors. MALORNY and ORZECHOWSKI have applied this theory to the antagonizing effect of veritol towards adrenaline on isolated intestine, and it seems to me that the above mentioned experiences with d-adrianol and d-corbasil may be well understood on the basis of this view. It may be presumed that d-adrianol has a rather great "Haftfähigkeit" to the sympathetic receptors, thus blocking them without stimulating them and therefore without affecting the intestinal motility. d-Corbasil on the other hand has too little "Haftfähigkeit" to the receptors to block them and therefore the action of adrenaline is not decreased.

The peculiar fact that the inhibiting action of l-corbasil contrary to that of l-adrenaline or l-adrianol is not abolished by d-adrianol remains unexplained. However, during the above

mentioned investigation of the influence of sympathicolytica on the smooth muscle actions of adrenaline substitutes it has been found that generally it is more difficult to antagonize the inhibiting action of l-corbasil on isolated intestine with sympathicolytic drugs than that of l-adrenaline or l-adrianol.

As far as the present author knows, it has not been found previously that one optical isomer of a drug, itself being inactive, completely abolishes the action of the other isomer.

The inhibiting effects on isolated intestine of on the one hand adrianol and corbasil and on the other sympatol and ephedrine are qualitatively quite different, which is evident already from their different appearances. CHEN and SCHMIDT explain the inhibiting effect of ephedrine by the assumption that ephedrine stimulates the sympathetic nerve endings. Contrary to this TAINTER and SEIDENFELD interpret the inhibiting effect of sympatol as caused by muscular depression; the same view is held by KINOSHITA as to the action of large doses of ephedrine. In agreement with these authors I consider the inhibiting effect of sympatol and ephedrine on isolated intestine as due not to stimulation of the sympathetic nerve endings but to direct muscular depression accompanied by blocking of the sympathetic receptors.

Summary.

1. The action of the optical isomers of adrianol, corbasil, sympatol and ephedrine on isolated rabbit's intestine has been studied.

2. The l-isomers of adrianol, corbasil and sympatol inhibit the intestine in all conc., whereas the d-isomers stimulate the intestine in small doses and inhibit it in larger ones.

3. The l-isomers of adrianol, corbasil and sympatol have a greater inhibiting activity than the d-isomers. Thus l-adrianol is 10 000 times as active as d-adrianol, l-corbasil 200 times as active as d-corbasil and l-sympatol 2 times as active as d-sympatol.

4. l-, dl- and d-Ephedrine are equally active on isolated intestine, stimulating it in small doses and inhibiting it in larger ones.

5. Considering the stimulating effect of d-adrianol, d-corbasil and d-sympatol on the intestine as well as the different ratios between the activities of the isomers on blood pressure respective

on isolated intestine, it is concluded that there is a *qualitative* difference in the mode of action of the optical isomers of the investigated drugs.

6. Without itself affecting the motility of the intestine d-adrianol abolishes the inhibiting effect of l-adrenaline and l-adrianol but does not diminish the response to l-corbasil.

7. The theoretical interpretation of the different pharmacodynamical action of enantiomorphic compounds is discussed.

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