added. At the appropriate times, 100 μL of the enzyme digestion solution was removed, diluted with 0.5 mL of a pH 2.2 sodium citrate buffer, and frozen until analysis. A check showed that no differences occurred between samples that were stored and otherwise identical samples that were analyzed immediately. The amounts of Leu and Gly-Ile (retention time 58.3 min on the Beckman 119 amino acid analyzer) were quantitated by amino acid analysis, and the amount of hydrolysis was computed by using the previously calculated peptide/Leu ratio. For each experiment 2.42 units of enzyme were used. The substrate concentrations were as follows: **4**, 2.49 mM; **5**, 2.93 mM; and **6**, 2.88 mM.

Acknowledgment. This work was supported by grants from the National Institute of General Medical Sciences and the National Science Foundation.

Registry No. **4**, 92642-54-1; **5**, 92642-55-2; **6**, 92642-56-3; **7**, 85701-35-5; **8**, 21277-16-7; **9**, 98-79-3; DCU, 2387-23-7; Gly-Ile, 19461-38-2; pyroglutamylaminopeptidase, 9075-21-2.

Potentiation of Fasciolicidal Agents by Benzoyl Side Chains. Synthesis of Benzoylsalicylanilides

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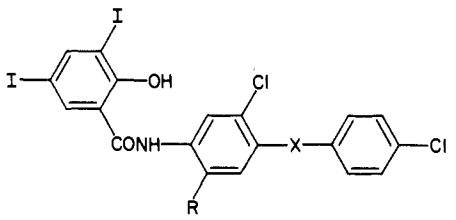
The synthesis and potent fasciolicidal activity of novel salicylanilides, with benzoyl substituents in the salicyl ring, is described. Several compounds surpassed the activity of commercially used flukicides against *Fasciola hepatica* infections in rats. Compounds **10**, **11**, and **15** were poorly active against the parasite in sheep and inactive in infected calves. It is concluded that the benzoyl substituents potentiate antiparasitic action by virtue of their electron-withdrawing properties rather than by advantageous protein binding at parasite receptor sites. Poor activity in sheep is ascribed to in vivo reduction of the carbonyl in the benzoyl group of the anilides.

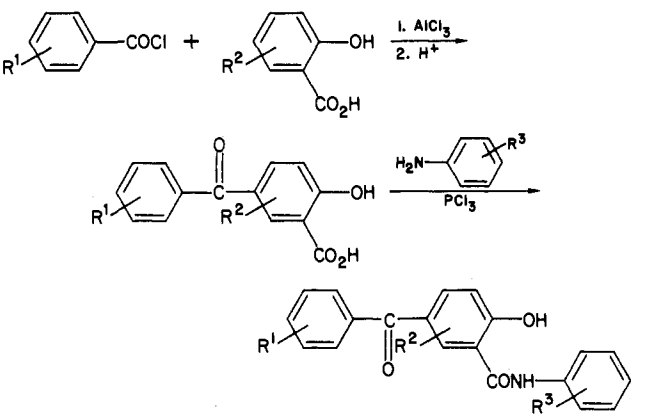
The treatment and prophylaxis of liver fluke infections in farm animals which are caused by the parasite *Fasciola hepatica* is an important objective in animal husbandry. Animals with fluke infections are in poor condition, fail to gain weight and have damaged livers. The parasite is mainly controlled in sheep by oral dosing with salicylanilide derivatives.[1] Improved fasciolicidal activity of salicylanilides has been achieved by the incorporation of an aryl side chain in the aniline moiety of the anilide, such as in rafoxanide[2] (**1**) salantel[3] (**2**), and closantel[4] (**3**). Similar substitution of a dihedral lipophilic aryl side chain in other antiparasitic agents, e.g., anthelmintic benzimidazolyl carbamates[5] and anticoccidial azauracils,[6] has also led to the potentiation of antiparasitic activity. We report the synthesis of novel salicylanilides with aryl side chains in the salicyl ring of the anilide (Tables I and II). More potent salicylanilides with a large therapeutic ratio could be dosed at high enough levels in infected animals to kill immature as well as adult liver fluke.



1, X=O; R=H
2, X=CO; R=H
3, X=CHCN; R=CH_3

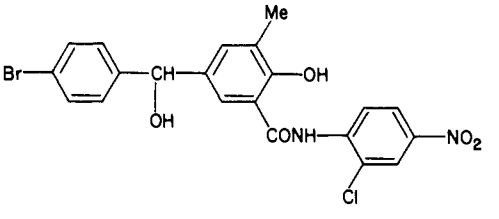
Chemistry. The anilides described in Tables I and II were prepared (Scheme I) by reaction of an appropriately substituted salicylic acid and an aniline in boiling chlorobenzene, in the presence of phosphorus trichloride. The substituted salicylic acids required to prepare compound

Scheme I



R^1=Br, Cl, CN, I, or NO_2
R^2=H, Me, or Bu^t
R^3=Br, Cl, CF_3, CN, or NO_2

6 and **7** were a gift from ICI Organics Division. The remaining acids (Table III) were synthesized by Friedel–Crafts acylation with substituted benzoyl halides into commercially available salicylic acids dissolved in nitrobenzene and in the presence of anhydrous aluminum chloride. Product isolation in high yield and purity was facilitated by the discovery that sodium salts of benzoylsalicylic acids were lipophilic and insoluble in sodium bicarbonate solutions. The preparation of the 3-*tert*-butyl acid **31** was carried out in dichloroethane below 5 °C and with excess acyl halide, because reaction in nitrobenzene caused loss of the *tert*-butyl group. Reduction of the anilide **11** with sodium borohydride afforded the benzyl alcohol **34**.



34

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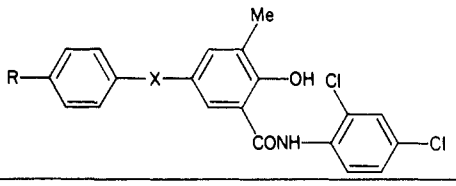
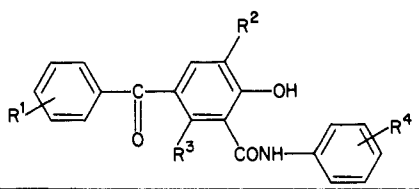
Table I. 2′,4′-Dichlorosalicylanilides



compd	R	X	mp, °C	recryst solvent	yield, %	formula[a]	fasciolicidal dose rat, mg/kg sc
4	NO_2	CO	215–216	AcOH	34	$C_{21}H_{14}Cl_2N_2O_5$	12.5
5	Br	CO	202–203	EtOAc	29	$C_{21}H_{14}BrCl_2NO_3$	100
6	H	CH_2	110–112	petrol	81	$C_{21}H_{17}Cl_2NO_2$	100
7	H	O	132–134	petrol	41	$C_{20}H_{15}Cl_2NO_3$	100
1	rafoxanide					$C_{19}H_{11}Cl_2I_2NO_3$	12.5

[a] The analysis of C, H, and N for all compounds was within ±0.4% of the calculated values.

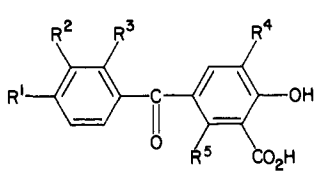
Table II. Benzoylsalicylanilides



compd	R^1	R^2	R^3	R^4	mp, °C	yield, %	formula[a]	fasciolicidal dose rat, mg/kg sc
8	4-NO_2	Me	H	2′-Cl, 4′-NO_2	254–255	9	$C_{21}H_{14}ClN_3O_7$	6.3
9	4-CN	Me	H	2′-Cl, 4′-NO_2	229–230	22	$C_{22}H_{14}ClN_3O_5$	6.3
10	4-Cl	Me	H	2′-Cl, 4′-NO_2	237–240		$C_{21}H_{14}Cl_2N_2O_5$	6.3
11	4-Br	Me	H	2′-Cl, 4′-NO_2	253–255	31	$C_{21}H_{14}BrClN_2O_5$	3.1
12	4-I	Me	H	2′-Cl, 4′-NO_2	260–261	25	$C_{21}H_{14}ClIN_2O_5$	12.5
13	4-Cl	H	H	2′-Cl, 4′-NO_2	263–264	32	$C_{20}H_{12}Cl_2N_2O_5$	25.0
14	4-Cl	Me	Me	2′-Cl, 4′-NO_2	164–166	23	$C_{22}H_{16}Cl_2N_2O_5$	3.1
15	4-Cl	Bu^t	Me	2′-Cl, 4′-NO_2	173–175	16	$C_{25}H_{22}Cl_2N_2O_5$	1.6
16	3-Cl, 4-Cl	Me	H	2′-Cl, 4′-NO_2	229–230	72	$C_{21}H_{13}Cl_3N_2O_5$	3.1
17	2-Cl, 4-Cl	Me	H	2′-Cl, 4′-NO_2	165–167	9	$C_{21}H_{13}Cl_3N_2O_5$	6.3
18	4-Cl	Me	H	2′-CF_3, 4′-NO_2	188–190	17	$C_{22}H_{14}ClF_3N_2O_5$	6.3
19	4-Cl	Me	H	2′-Br, 4′-NO_2	259–260	35	$C_{21}H_{14}BrClN_2O_5$	3.1
20	4-Cl	Me	H	2′-CF_3, 4′-Br	194–196	19	$C_{22}H_{14}BrClF_3NO_3$	6.3
21	4-Cl	Me	H	3′-Cl, 5′-Cl	190–192	9	$C_{21}H_{14}Cl_3NO_3$	100
22	4-Cl	Me	H	3′-Cl, 4′-Cl	233–234	23	$C_{21}H_{14}Cl_3NO_3$	100
23	4-Cl	Me	H	4′-CN	227–228	11	$C_{25}H_{15}ClN_2O_3$	100

[a] The analysis for C, H, and N for all compounds was within ±0.4% of the calculated values.

Table III. 5-Benzoylsalicylic Acids



compd	R^1	R^2	R^3	R^4	R^5	mp, °C	yield, %	formula[a]
24	NO_2	H	H	Me	H	247–248	74	$C_{15}H_{11}NO_6$
25	CN	H	H	Me	H	227–230	18	$C_{16}H_{11}NO_4$
26	Cl	H	H	Me	H	223–224	76	$C_{15}H_{11}ClO_4$
27	Br	H	H	Me	H	204–206	64	$C_{15}H_{11}BrO_4$
28	I	H	H	Me	H	206–208	38	$C_{15}H_{11}IO_4$
29	Cl	H	H	H	H	220–222	37	$C_{14}H_{19}ClO_4$
30	Cl	H	H	Me	Me	185–187	7	$C_{16}H_{13}ClO_4$
31	Cl	H	H	Bu^t	Me	168–170	29	$C_{19}H_{19}ClO_4$
32	Cl	Cl	H	Me	H	245–246	57	$C_{15}H_{10}Cl_2O_4$
33	Cl	H	Cl	Me	H	215–217	56	$C_{15}H_{10}Cl_2O_4$

[a] The analysis for C, H, and N for all compounds was within ±0.4% of the calculated values.

Biological Results and Discussion

Initial test results (Table I) against *F. hepatica* infections in rats indicated that good fasciolicidal activity could be discovered by placing dihedral side chains in the salicyl ring of salicylanilides. Thus the nitro derivative **4** had fasciolicidal activity of the same order as rafoxanide (**1**). The presence of a lipophilic aryl side chain in other molecules such as **6** and **7** did not confer activity. This suggested that the claim[6] that these side chains might have a common role in antiparasitic agents of enhancing protein

binding to a parasite receptor site was not valid in this series. Consideration of the Hammett aromatic substituent constants[7] for the aryl side chains of compounds in Table I indicated that fasciolicidal activity was related to the electronic effect of the side chain. Compounds containing the electron-withdrawing benzoyl group (**4** and **5**) were active whereas the electron-donating side chains afforded inactive derivatives. This view that acidity is important in defining fasciolicidal activity is supported by knowledge that salicylanilides are acidic uncouplers of oxidative phosphorylation[8] and this is their likely mode of fasciolicidal action.[9] It could be argued that compound **6** and **7** may not be flukicides because they are hydroxylated in vivo at the free para position of their aryl side chain and thereby deactivated or eliminated. This possibility was not explored. Further derivatives of the very active benzoylsalicylanilides were prepared (Table II). Compounds **8** and **11** with greater potency than rafoxanide (**1**) were obtained when the electron-withdrawing nitro group was incorporated into the aniline moiety of the active compounds reported in Table I. It is known[10] that alkyl substitution of the salicyl ring of salicylanilides leads to better flukicides and in this series there was a progressive increase in potency as alkyl substitution was increased (**11**, **13–15**). This increase in activity as lipophilic groups are placed close to acidic protons in flukicides has also been reported for the phenylazomalononitrile fasciolicides.[11] Placing additional substituents in the benzoyl group (**16** and **17**) afforded active compounds but without significantly improved activity. The only anilides of potential commercial value were those with strong electron-withdrawing substituents in the aniline ring. Thus compounds **18–20** had activity whereas **21–23** were of no value, illustrating the importance of balancing the electron-withdrawing properties of substituents on either side of the anilide to get optimum acidity for the anilide.

The anilides **10**, **11**, and **15** (Table II) were not toxic to rats on acute oral dosing at 50 times their effective oral fasciolicidal dose, which was found to be twice the sc dose reported in Table II. Due to the high potency and unusually large therapeutic ratio found for these compounds, they were tested by oral gavage in sheep with adult liver fluke infections.

Compounds **10**, **11**, and **15** all reduced fecal egg output from infected sheep at oral doses of 10 mg/kg at 7 days after dosing. For example, the egg output for anilide **11** was 255 before dosing but 7 days after treatment had fallen to 10. These falls in egg production were not sustained however and rose to 100 at 14 days and 165 after 21 days. Thus oral dosing of these anilides to infected sheep reduced egg output, but the fluke subsequently recovered and were not eradicated. This contrasts with results for rafoxanide (**1**), which eliminated egg production at 14 days after a 7.5 mg/kg oral dose in similarly infected sheep. In commercial animal husbandry it is essential that a fasciolicide is effective at a single acute dose as chronic drug dosing would require regular rounding up of the sheep. When anilide **11** was dosed subcutaneously at 5 mg/kg in calves infected with *F. hepatica*, fecal egg production was unchanged at 7 and 14 days after dosing, so that no fasciolicidal activity was found. For these reasons compounds in Table II were not developed commercially.

The rat test for flukicides is predictive of the fasciolicidal activity found for all commercially available flukicides including anilides such as **1**. It is thus of interest to consider why it failed in this case. Anilides in Table II kill *F. hepatica* in vitro and in vivo in rats. This suggests that insufficient drug reaches the parasite in the bile duct of sheep which could be due to poor absorption of drug or detoxication of the drug by the sheep. Subcutaneous injection of anilides such as **11** at 10 mg/kg in infected sheep gave similar results to those obtained by oral dosing. This suggested that drug absorption was not the problem with these compounds and that they were being detoxified by the sheep. It is known that other antiparasitic agents that contain benzoyl groups such as anthelmintics[12] and anticoccidials[13] are metabolized in vivo by reduction to the corresponding benzyl alcohols. The carbonyl group of anilide **11** was reduced chemically to give the benzyl alcohol **34**, which was not fasciolicidal in vitro or in vivo in rats and sheep. It is thus suggested that the salicylanilides in Table II are not active in sheep because they are reduced in vivo to alcohol derivatives that are not sufficiently acidic to be fasciolicidal.

Conclusion

The incorporation of benzoyl side chains into the salicyl ring of salicylanilides leads to very potent anilides with large therapeutic ratios in the rat. These compounds are only active when they are sufficiently acidic. Metabolic detoxication in sheep reduces their acidity so that they lose significant fasciolicidal activity in this species. Thus the placement of dihedral aryl side chains in salicylanilides only affords potent fasciolicides when these side chains are electron-withdrawing groups thereby making the anilide sufficiently acidic. The aryl side chains do not give potentiation of antiparasitic action by advantageous binding to parasite receptor proteins but are more lipophilic alternative substitutents to other electron-withdrawing groups such as nitro[10] or cyano,[15] which are salicyl ring substituents in known fasciolicidal anilides.

Experimental Section

Melting points are uncorrected. IR and NMR were determined on a Perkin-Elmer 157 and a Varian HA 100 spectrometer, respectively. Spectral data were consistent with the assigned structures. Elementary analyses were within ±0.4% of the theoretical values. Compounds in Tables I–III were prepared by the following general methods. Recrystallization of compounds in Table II was from glacial HOAC and for Table III petrol–EtOAc. Petrol was petroleum ether, bp 60–80 °C.

5-(4-Bromobenzoyl)-2′-chloro-3-methyl-4′-nitrosalicylanilide (**11**). 5-(4-Bromobenzoyl)-3-methylsalicylic acid (11.7 g, 35 mmol), 2-chloro-4- nitroaniline (6.0 g, 35 mmol), and phosphorus trichloride (1.0 mL, 11.5 mmol) were heated under reflux for 5 h in PhCl (140 mL). The PhCl was concentrated to half-volume and cooled. The separated solid was collected and crystallized from AcOH to give **11** (5.3 g, 31%).

5-(4-Bromobenzoyl)-3-methylsalicylic Acid (**27**). $AlCl_3$ (15.9 g, 120 mmol) was added to stirred $PhNO_2$ (60 mL) cooled by ice–H_2O. After 5 min 3-methylsalicylic acid (9.1 g, 60 mmol) was added, and after the vigorous reaction subsided (10 min), 4-bromobenzoyl chloride (13.2 g, 61.25 mmol) was added during 20 min. The mixture was stirred on a steam bath for 1 h and allowed to cool. The mixture was poured on to ice and acidified with 2 N HCl. An EtOAc extract was stirred with excess $NaHCO_3$ solution and the solid that separated collected and acidified with 2 N HCl. The solid was collected and crystallized from petrol–

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EtOAc to give **27** (12.8 g, 64%).

3-*tert*-Butyl-5-(4-chlorobenzoyl)-6-methylsalicylic Acid (31). $AlCl_3$ (7.8 g, 58.9 mmol) and 4-chlorobenzoyl chloride (10.8 g, 61.5 mmol) were added to $ClCH_2CH_2Cl$ (60 mL) at room temperature. When solution occurred, the stirred mixture was cooled to −5 °C and 3-*tert*-butyl-6-methylsalicylic acid (6.3 g, 29 mmol) suspended in $ClCH_2CH_2Cl$ (15 mL) added. After 40 min at −5 °C the mixture was poured on to ice and acidified with 2 N HCl. Extraction with $CHCl_3$ and evaporation gave an oil. Extraction of the oil with boiling petrol gave on evaporation **31** (3.0 g, 29%).

5-(4-Bromo-α-hydroxybenzyl)-2′-chloro-3-methyl-4′-nitrosalicylanilide (34). $NaBH_4$ (1.0 g, 26.3 mmol) and **11** (1.0 g, 2.0 mmol) were added to EtOH (100 mL), and the mixture was stirred for 18 h. The mixture was acidified with 2 N HCl and the solid precipitate collected. The solid was washed with H_2O and dried to give **34** (800 mg, 80%), mp 193–195 °C. Anal. ($C_{21}H_{16}BrClN_2O_5$) C, H, N.

Fasciolicidal Activity. Activity in vitro was detected by incubating two adult fluke (from rats) in Hedon-Fleig solution (10 mL). Test compounds (5 ppm) were administered in Me_2SO (50 μL or less), and if the fluke did not move, the compounds were active. Compounds in Tables I and II were tested by a single sc injection in lissapol in rats at the doses indicated. Rats were previously infected with 20 metacercariae and dosed at 12 weeks postinfection. The rats were examined 5 days later and compounds that removed 90% of the fluke from the bile duct were considered active. Sheep infected with 250–300 metacercariae were kept until they were passing fluke eggs. The sheep were dosed with compound (10 mg/kg) by oral gavage and egg counts made on midday fecal samples on days 0, 7, and 14 after dosing. Compounds completely suppressing fluke egg production on day 14 were taken to be active against adult liver fluke in sheep. Details of the tests have been reported.[14]

Registry No. **4**, 92524-64-6; **5**, 92524-65-7; **6**, 92524-66-8; **7**, 92524-67-9; **8**, 92524-68-0; **9**, 92524-69-1; **10**, 92524-70-4; **11**, 92524-71-5; **12**, 92524-72-6; **13**, 92524-73-7; **14**, 92524-74-8; **15**, 92524-75-9; **16**, 92524-76-0; **17**, 92524-77-1; **18**, 92524-78-2; **19**, 92524-79-3; **20**, 92524-80-6; **21**, 92524-81-7; **22**, 92524-82-8; **23**, 92524-83-9; **24**, 92524-84-0; **25**, 92524-85-1; **26**, 92524-86-2; **27**, 92524-87-3; **28**, 92524-88-4; **29**, 92524-89-5; **30**, 92524-90-8; **31**, 92524-91-9; **32**, 92524-92-0; **33**, 92524-93-1; **34**, 92524-94-2; 2-Cl, $4\text{-}NO_2C_6H_3NH_2$, 121-87-9; $2\text{-}CH_3$, $4\text{-}NO_2C_6H_3NH_2$, 121-01-7; 2-Br, $4\text{-}NO_2C_6H_3NH_2$, 13296-94-1; $2\text{-}CF_3$, $4\text{-}BrC_6H_3NH_2$, 445-02-3; $3,5\text{-}Cl_2C_6H_3NH_2$, 626-43-7; $3,4\text{-}Cl_2C_6H_3NH_2$, 95-76-1; $4\text{-}CNC_6H_4NH_2$, 873-74-5; $4\text{-}NO_2C_6H_4COCl$, 122-04-3; $4\text{-}CNC_6H_4COCl$, 6068-72-0; $4\text{-}ClC_6H_4COCl$, 122-01-0; $4\text{-}BrC_6H_4COCl$, 586-75-4; $4\text{-}IC_6H_4COCl$, 1711-02-0; $3,4\text{-}Cl_2C_6H_3COCl$, 3024-72-4; $2,4\text{-}Cl_2C_6H_3COCl$, 89-75-8; 3-methylsalicylic acid, 83-40-9; salicylic acid, 69-72-7; 3,6-dimethylsalicylic acid, 3921-12-8; 3-*tert*-butyl-6-methylsalicylic acid, 6934-03-8.

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Reactivators of Organophosphorus-Inhibited Acetylcholinesterase. 1. Imidazole Oxime Derivatives

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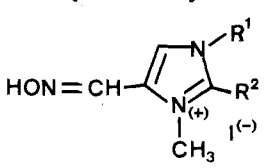
Received July 25, 1983

4-[(Hydroxyimino)methyl]-3-methylimidazolium iodides were prepared and tested for their reactivating potency on acetylcholinesterase inhibited by tetraethyl pyrophosphate (TEPP). The in vitro testing revealed that the new compounds are weak reactivators of the phosphorylated electrophorus acetylcholinesterase.

Since the discovery of oximes[1] as potent reactivators of organophosphorus-inhibited acetylcholinesterase (acetylcholine hydrolase, EC 3.1.1.7, AcChE), 2-pyridine aldoxime methiodide (2-PAM)[2] has been found to be particularly effective, and most oximes assayed as potential reactivators have been modeled after this aldoxime. Many *N*-pyridinium derivatives of 2-PAM have thus been investigated[3-6]. Derivatives where the pyridine ring has been substituted by other N-heterocycles are also described as AcChE reactivators[5,7-10].

The aim of this work was the synthesis and biological screening of 1-aryl(alkyl)-4-[(hydroxyimino)methyl]-3-methylimidazolium iodides (**1a–f**) and 1-aryl(alkyl)-4-[(hydroxyimino)methyl]-3-methyl-2-(methylthio)-imidazolium iodides (**2a–f**) in order to collect experimental data for QSAR analysis of this group of compounds.



R^2= H (Series 1)
R^2= MeS (Series 2)

a R^1= 4-EtOPh
b R^1= 4-MeOPh
c R^1= 4-MePh
d R^1= Ph
e R^1= Et
f R^1= Allyl

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‡Departamento de Bioquimica.

Chemistry. The synthesis of the compounds **1a–f** and **2e–f** was accomplished by methylation of 4-formylimidazole derivatives[11] with methyl iodide and subsequent condensation with hydroxylamine. In this reaction a single product, the *Z* isomer, was usually isolated. Only in the case of **2f** did the oximation reaction give geometrical isomers which separated by fractional recrystallization.

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