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CHROMATOGRAPHIC SEPARATION OF ISOMERIC FORMS OF A TETRADENTATE SCHIFF BASE DERIVED FROM 1,1,1-TRIFLUORO-5,5-DIMETHYLHEXANE-2,4-DIONE AND 1,2-DIAMINOETHANE

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SUMMARY

Reaction between the asymmetrical β -diketone 1,1,1-trifluoro-5,5-dimethylhexane-2,4-dione with 1,2-diaminoethane gives, among other products, two distinct tetradentate ketoenamine isomers. These compounds have been separated chromatographically from the numerous reaction products and identified. The major product of the reaction was the dihydrodiazepin derivative. Some properties of the isomers are given.

INTRODUCTION

When tetradentate Schiff bases are formed in reactions between asymmetrical β -diketones and symmetrical aliphatic diamines, it is possible for three isomeric tetradentate species to be formed. In work which has been reported to date, these condensation reactions have been depicted as occurring exclusively at the carbonyl group adjacent to the more passive substituent of the β -diketone. Thus, it appears that benzoylacetones^{1,2} and trifluoroacetylacetone^{3,4} condense with 1,2-diaminoethane exclusively at the carbonyl group attached to the methyl group. Furthermore, other isomeric forms of such Schiff bases have not been described presumably because the synthetic methods which circumvent this selective condensation process have yet to be applied.

In this paper, we report the first synthesis of the tetradentate Schiff bases obtained by condensing 1,1,1-trifluoro-5,5-dimethylhexane-2,4-dione (HTPM) and 1,2-diaminoethane. From the product, two geometrical isomers were isolated. Due emphasis is given to the essential role of the chromatographic process in demonstrating the existence and facilitating the separation of the two isomers from a number of by-products before characterization and structure determination was possible.

EXPERIMENTAL

General

All solvents were redistilled and dried commercially available compounds.

Silica gel for column chromatography (May & Baker, Dagenham, Great Britain) was prepared by sequential treatment with methanol, ethyl acetate and hexane (200–300 ml each) before use. For thin-layer chromatography (TLC) silica gel (Merck, Darmstadt, G.F.R.) layers were air-dried (3–4 days) and used without activation.

Visualizing reagents⁵ used for TLC were as follows: Ehrlich's reagent (0.5% dimethylaminobenzaldehyde with 1.5% hydrochloric acid in butanol–ethanol mixture (4:1, v/v); ninhydrin reagent (0.5% solution in butanol, w/v); copper acetate reagent (0.5% solution in water, w/v).

Reaction products were examined by gas chromatography (GC) (Packard-Becker Model 417 gas chromatograph) employing coiled stainless-steel columns (1 m × 4 mm O.D.) packed with Chromosorb W (HP, 100–120 mesh, DMCS-treated) coated with 10% SE-30. The nuclear magnetic resonance (NMR) spectral data were obtained on a Varian A60 instrument, and the results are quoted on the δ -scale relative to tetramethylsilane.

Synthesis of Schiff base material

The β -diketone (HTPM; 20 g, 0.10 mole), prepared as previously^{6,7} described, was dissolved in absolute ethanol (20 ml) and added slowly (30 min) to a solution of 1,2-diaminoethane (1.5 g, 0.025 mole) in absolute ethanol (20 ml) while heating and stirring on a water-bath. Following a further period of heating (1 h), excess solvent and β -diketone were removed under vacuum and the viscous, amber liquid held in a vacuum desiccator (4 h, 0.02 Torr) for the removal of the last traces of the β -diketone. This product was treated on a column of silica gel (20 × 5 cm I.D.), eluting with hexane–benzene (1:1, 600 ml) and benzene (200 ml). The combined eluates yielded a very viscous, clear, pale-amber coloured liquid with a pleasant, sweet odour. This material was shown by TLC to be a mixture of at least three compounds. Further development of the column with benzene, ethyl acetate and methanol gave, on removing the solvents, a buff-coloured solid. When recrystallized, the white product was subsequently identified as the dihydrodiazepin derived from the β -diketone and diamine.

Isolation of isomers

The Schiff base mixture was treated on a semi-preparative scale of TLC using silica gel layers (20 cm × 20 cm × 1 mm thickness) and hexane–benzene (1:1, one or two developments) as solvent. The compounds of interest (Bands 3, 4 and 6, see Table I) were recovered as discrete bands from several plates and removed from the adsorbent with a suitable solvent (dichloromethane or ethyl acetate).

Schiff base, Isomer 1. This was isolated by TLC as Band 4 and as a viscous, pleasant-smelling pale yellow liquid showing no evidence of crystallizing (after two weeks in an evacuated desiccator). GC confirmed the presence of only a single compound with retention time of approx. 20 min (see Fig. 1). Microanalysis: found C 51.8, H 5.8, N 6.2%; $C_{18}H_{26}N_2F_6O_2$ requires C 51.9, H 6.3, N 6.7%.

Schiff base, Isomer 2. This was isolated as Band 6, and was similar to Isomer 2 in general properties. It, too, gave a single GC peak retention time of approx. 24.5 min (see Fig. 1). Microanalysis: found C 51.3, H 6.0, N 7.1%.

Band 3 was isolated for identification because of its ready reaction with cupric

ions to form a green compound and its large R_F value. It gave a single GC peak with retention time approx. 31 min. Microanalysis: found C 57.3, H 6.3, N 6.3%.

RESULTS AND DISCUSSION

Chromatographic examination of the crude reaction product has revealed that attempts to produce a Schiff base from condensation of 1,2-diaminoethane and HTPM produced no fewer than seven reaction products. Comparison with previously reported syntheses of related tetradentate Schiff bases is not possible, and in normal circumstances such studies are not undertaken because, we believe, of the ease with which the desired base can be crystallized from the reaction mixture, and purified. Where this is not the case, metal chelates derived from the base can be prepared and purified^{8,9}. However, in an exceptional study, Richardson and Sievers¹⁰ examined, and reported in considerable detail, a number of products obtained in attempts to form the tetradentate Schiff base from 1,1,1,5,5,5-hexafluoro-2,4-pentanedione and 1,2-diaminoethane. This work did not, however, involve any chromatographic study of the reaction products.

In the present study, failure to isolate the expected crystalline product by the usual procedure^{3,11,12} led to a chromatographic examination of the reaction product. Initial examination by TLC proved particularly informative since, in addition to revealing an array of minor products detectable by nitrogen-sensing reagents, the observation of two well-separated violet compounds following the application of cupric acetate as a reagent immediately suggested that isomeric forms of the Schiff base had been produced. A summary of these observations is given in Table I, where the compounds are listed in decreasing order of R_F value together with identification of the principle products. By the combination of the three visualizing reagents it is possible to distinguish a greater number of compounds than is listed, however, the

TABLE I

TLC DATA FOR THE CRUDE SCHIFF BASE

Silica gel layers were developed with hexane-benzene (5:8, v/v).

Band No.	R_F	Reaction with visualizing reagents			Compound identity
		Ehrlich's reagent*	Ninhydrin**	Copper(II) acetate ^{§, §§}	
1	0.97	intense yellow	red-pink	no reaction	unknown
2	0.84	intense yellow	red-pink	no reaction	unknown
3	0.69	intense yellow	red-pink	green*	see text
4	0.44	intense yellow**	red-pink	violet***	Isomer 1
5	0.19	intense yellow	red-pink	no reaction	unknown
6	0.12	intense yellow**	red-pink	violet***	Isomer 2
7	0.0	faint yellow	orange	light green	dihydrodiazepin

* Colour develops within 1-2 min of applying reagent.

** Colour develops after heating at 100°.

*** As for *; colour changes slowly on plates (over 2-3 days) to green.

§ In the presence of excess β -diketone, a pale blue colour due to the copper chelate extends as a streak to $R_F \sim 0.4$.

§§ Nickel or cobalt acetates may be used, but without advantage.

majority of these are nitrogenous species and seemingly unreactive to cupric ions. It may be noted that silica gel was superior to alumina for the TLC work.

A property which is not readily evident from the data of Table I is the surprisingly low polarity (or hydrogen-bonding capability) of the Schiff base(s), since these compounds can be eluted or developed with hexane–benzene mixtures on silica gel adsorbents. In contrast, the Schiff base derived from 1,1,1-trifluoropentane-2,4-dione and 1,2-diaminoethane required totally different solvent systems (consisting of ethyl acetate–methanol mixtures) for satisfactory migration. The presence of a *tert.*-butyl group is not sufficient to explain this property since elution of the related, non-fluorinated Schiff base derived from 2,2-dimethylhexane-3,5-dione required ethyl acetate–benzene solvent systems for adequate migration. It is also an unexpected finding in view of previous observations¹² regarding the influence of trifluoromethyl substituents in structures of this type.

GC data confirmed the presence of the numerous reaction products and showed their relationship to the individual bands isolated from the silica gel layers. A typical, temperature-programmed chromatogram is given in Fig. 1. The major product is seen to be the dihydrodiazepin. The additional information conveyed in the chromatogram is the relative proportions and properties of the various volatile products. Some variation of the reaction conditions did not affect the number of products formed but the proportion of Isomer 1 to Isomer 2 changed and the dihydrodiazepin was always in highest yield. It remains for a systematic kinetic study to be carried out for a clarification of the reaction mechanism, however, throughout the examination of the reaction products no evidence for the existence of the third isomer was found.

Isomers 1 and 2 are assigned the structures I and II, respectively, on the basis

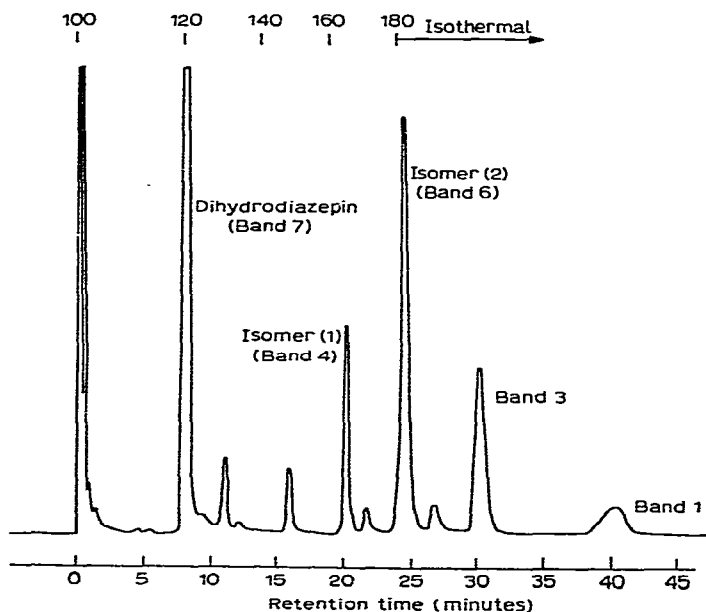
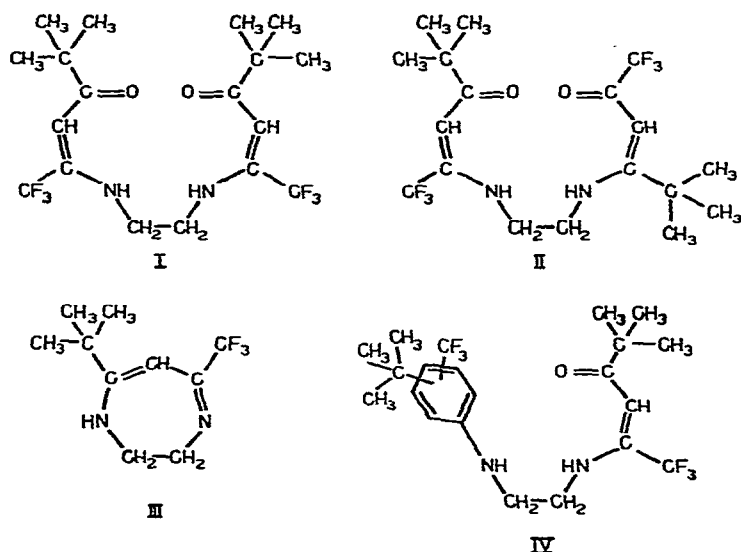


Fig. 1. A temperature-programmed chromatogram showing the Schiff base isomers and several reaction products. The relationship to the migration of the compounds in TLC is also indicated.



of extensive spectroscopic data, of which NMR was the most useful because of its clarification of both overall geometry and tautomeric structure. Band 7 is identified as the dihydrodiazepin (see structure III), and as for the other compounds, on the evidence mainly of NMR and mass spectrometry, Band 3 is assigned structure IV. Although the detailed rationalization of these structures will be presented elsewhere, a summary of the NMR data is given in Table II.

Of relevance to this work is our isolation¹³ of the nickel(II) and copper(II) chelates of the two isomers, and the observation that their volatilities and GC elution from non-polar columns parallel the volatilities of the two isomers as shown in Fig. 1.

TABLE II
SUMMARY OF NMR DATA FOR SCHIFF BASE ISOMERS AND OTHER REACTION PRODUCTS

Chemical shifts measured in CDCl_3 downfield from tetramethylsilane. Correct proton counts were found for each signal.

Proton	Chemical shift (δ)			
	Isomer 1	Isomer 2	Dihydrodiazepin(III)	Compound IV
Tert.-Butyl	1.15	1.17 and 1.33	1.20	1.17 and 1.30
Methine	5.75	5.54 and 5.79	5.02	5.78
Methylene	$\sim 3.50^*$	$\sim 3.70^*$	3.31 and 3.88	$\sim 3.48^*$
Imine	10.30	10.30 and 11.67	5.85	3.93 and 10.40
Aromatic	—	—	—	6.67, 6.82 and 7.02

* The signal consists of a complex multiplet centred at this value.

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