DERIVATIVES OF *p*-AMINOACETOPHENONE WITH JUVENILE HORMONE ACTIVITY

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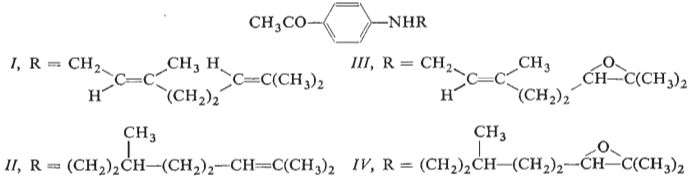
Alkylation of N-trifluoroacetyl-*p*-aminoacetophenone with geranyl bromide and citronellyl bromide and subsequent alkaline hydrolysis resulted in N-(3,7-dimethyl-2,6-octadienyl)-(*I*) and N-(3,7-dimethyl-6-octenyl)-(*II*) derivatives of *p*-aminoacetophenone. Epoxidation of the intermediates and subsequent hydrolysis yielded further N-(6,7-oxido-3,7-dimethyl-2-octenyl)-(*III*) and N-(6,7-oxido-3,7-dimethyloctyl)-(*IV*) derivatives of *p*-aminoacetophenone.

In connection with the preparation of biologically active compounds with the activity of the insect juvenile hormone, derivatives *I*–*IV* of *p*-aminoacetophenone were synthesized.



Preliminary experiments showed that the alkylation methods used for the preparation of secondary aromatic amines[1,2] are not suitable for the synthesis of derivatives *I*–*IV* as poorly resolvable mixtures of reaction products are formed. Moreover, geranyl bromide, used as one of the starting compounds, is unstable at higher temperatures[3]. Alkylation with halogen derivatives at the nitrogen proceeds readily with the acyl derivatives of the primary amines[4,5]. For this reason, for the preparation of the above compounds N-trifluoroacetyl-*p*-aminoacetophenone was used; the trifluoroacetyl group can be removed from the intermediates formed by gentle alkaline hydrolysis[6,7].

The starting *p*-nitroacetophenone was hydrogenated in the presence of platinum to convert it to *p*-aminoacetophenone which reacted with trifluoroacetanhydride in ether to yield N-trifluoroacetyl-*p*-aminoacetophenone. This reacted with sodium

methanolate in methanol to the sodium salt. The reaction of the sodium salt with geranyl bromide in dimethylformamide proceeded already at room temperature, with citronellyl bromide at 70–80°C, and both resulted in homogeneous products. The trifluoroacetyl group was removed from the products by the action of an aqueous-ethanolic solution of sodium hydroxide (which is preferable to the reported[7] heating of trifluoroacetyl derivatives with an aqueous solution of sodium hydroxide).

Masking of the amine group of secondary amines *I* and *II* with trifluoroacetyl made it further possible to carry out epoxidation in the alkenyl chain with the aid of perphthalic acid and to obtain, after splitting off this masking group, compounds *III* and *IV*. In the case of the unprotected amino group, epoxidation resulted in a poorly resolvable mixture of reaction products.

EXPERIMENTAL

p-Aminoacetophenone

p-Nitroacetophenone (20 g, 0·121 mol) dissolved in 300 ml methanol was hydrogenated at room temperature in the presence of a catalytic amount of platinum (0·5 g PtO_2). The consumption of hydrogen was 10% higher than the theoretical amount. After termination of the reaction, the catalyst was removed by filtration and the solvent was evaporated from the filtrate. After a four-fold crystallization of the residue from benzene, a total of 12 g (73%) *p*-aminoacetophenone was obtained, m.p. 104–106°C (ref.[9] gives 103–105°C, ref.[10] gives 106–107°C). For C_8H_9NO (135·2) calculated: 71·08% C, 6·71% H, 10·36% N; found: 71·00% C, 6·88% H, 10·45% N.

N-Trifluoroacetyl-*p*-aminoacetophenone

10 g (0·05 mol) trifluoroacetanhydride in 5 ml ether was added dropwise over 30 min to a boiling solution of 1·35 g (0·01 mol) *p*-aminoacetophenone in 50 ml ether. The mixture was stirred for 30 min, the precipitate was filtered off, the filtrate was evaporated *in vacuo* and both fractions were recrystallized together from a mixture of ethanol–water (1 : 1) A total of 2·1 g (91·5%) N-trifluoroacetyl-*p*-aminoacetophenone was obtained (m.p. 160–161·5°C). The mass spectrum shows peaks at *m/e* 231(M) and 216. For $C_{10}H_8F_3NO_2$ (231·2) calculated: 51·95% C, 3·44% H, 6·06% N; found: 52·22% C, 3·55% H, 6·30% N. *The sodium salt*: 11·1 g (0·048 mol) N-trifluoroacetyl-*p*-aminoacetophenone was dissolved under stirring in 48 ml 1M solution of sodium methanolate in methanol. After 5 min of standing, ether was added dropwise under stirring as long as precipitate formed. This was then filtered and dried. A total of 12 g (99%) sodium salt of N-trifluoroacetyl-*p*-aminoacetophenone was obtained, with a melting point higher than 360°C. For $C_{10}H_7F_3NNaO_2$ (253·2) calculated: 47·45% C, 2·79% H, 5·53% N; found: 47·64% C, 3·01% H, 5·22% N.

N-Trifluoroacetyl-N-(3,7-dimethyl-2,6-octadienyl)-*p*-aminoacetophenone

Geranyl bromide[3] (2·8 g, 12·9 mmol) was added dropwise to a solution of a sodium salt of N-trifluoroacetyl-*p*-aminoacetophenone (1·7 g, 6·73 mmol) in 5 ml dimethylformamide and the mixture was stirred at room temperature for 23 h, diluted with 30 ml water and the product was extracted with ether. The ether layer was washed with water and dried with magnesium sulfate. The solvent was removed by evaporation *in vacuo*. The residue of 3·6 g was diluted with light petroleum and

filtration removed crystals of N-trifluoroacetyl-*p*-aminoacetophenone. The solvent was evaporated from the filtrate *in vacuo* and the residue was separated on a column of silica gel (elution with 20% ether in light petroleum). A total of 2·25 g (91·5%) product was obtained. Peaks of the mass spectrum at *m/e*: 367 (M), 324, 248, 231, 216 and 69. For elementary analysis the sample was redistilled *in vacuo* at 0·05 Torr and at a bath temperature 178°C. For $C_{20}H_{24}F_3NO_2$ (367·4) calculated: 65·38% C, 6·58% H, 15·51% F; found: 65·14% C, 6·78% H, 15·21% F.

N-Trifluoroacetyl-N-(3,7-dimethyl-6-octenyl)-*p*-aminoacetophenone

2·6 g (11·9 mmol) citronellyl bromide[8] was added dropwise to a solution of the sodium salt of N-trifluoroacetyl-*p*-aminoacetophenone (1·5 g, 5·93 mmol) in 5 ml dimethylformamide. The mixture was stirred and heated to 70—80°C for 5 h and then was processed as with the preceding compound. A total of 1·45 g (66·3%) product was obtained; the mass spectrum contains peaks at *m/e*: 369 (M), 354, 300, 284, 244, 232, 216, 138, 95 and 69. For analytical purposes, the sample was redistilled at 0·01 Torr and a bath temperature 175—178°C. For $C_{20}H_{26}F_3NO_2$ (369·4) calculated: 65·02% C, 7·09% H, 15·43% F; found: 64·48% C, 7·08% H, 15·37% F.

N-(3,7-Dimethyl-6-octenyl)-*p*-aminoacetophenone (*II*)

A mixture of N-trifluoroacetyl-N-(3,7-dimethyl-6-octenyl)-*p*-aminoacetophenone (0·25 g, 0·68 mmol), 10 ml 1M-NaOH and 6 ml ethanol was stirred for 7 h and heated to 50°C, and for further 15 h it was left at room temperature. The reaction mixture was then diluted with 10 ml water and the product was extracted with ether. After washing with water to a neutral reaction and after drying with magnesium sulfate, the ether was removed by evaporation and the residue was distilled *in vacuo*. A total of 0·14 g (75·5%) compound *II* was obtained, b.p. 172—173°C/0·01 Torr. The mass spectrum of *II* contains a molecular peak at mass 273 and further peaks at *m/e* 258, 148 and 135. For $C_{18}H_{27}NO$ (273·4) calculated: 79·05% C, 9·95% H, 5·12% N; found: 79·30% C, 10·32% H, 5·24% N.

N-(3,7-Dimethyl-2,6-octadienyl)-*p*-aminoacetophenone (*I*)

A mixture of 0·55 g (1·5 mmol) N-trifluoroacetyl-N-(3,7-dimethyl-2,6-octadienyl)-*p*-aminoacetophenone and 15 ml 1M-NaOH was homogenized with a minimum amount of ethanol and was left at room temperature for 17 h. Further procedure was as with the preparation of *II*. A total of 0·25 g amine *I* was obtained (62·5%), b.p. 174—175°C/0·01 Torr. Mass spectrum of *I* contains peaks at *m/e* 271 (M), 256, 148, 135, 120, 69. For $C_{18}H_{25}NO$ (271·4) calculated: 79·66% C, 9·28% H, 5·16% N; found: 79·68% C, 9·32% H, 5·03% N.

N-(6,7-Oxido-3,7-dimethyl-2-octenyl)-*p*-aminoacetophenone (*III*)

2·8 ml 0·9M ether solution of perphthalic acid was added to a solution of 0·9 g N-trifluoroacetyl-N-(3,7-dimethyl-2,6-octadienyl)-*p*-aminoacetophenone (2·45 mmol) in 5 ml ether. The mixture was left for 17 h at room temperature, then it was poured into 30 ml 1M-NaOH and stirred for 24 h at 35°C. The product was extracted with ether and, after washing with water to a neutral reaction and drying with magnesium sulfate, it was evaporated *in vacuo*. The residue of 0·5 g was separated on a column of silica gel (eluted with 20% ether in light petroleum), yielding 0·4 g (57%) compound *III*, which showed mass-spectrum peaks at *m/e* 287 (M), 272, 271, 244, 188, 148, 135, 120. For $C_{18}H_{25}NO_2$ (287·4) calculated: 75·22% C, 8·84% H, 4·87% N; found: 75·23% C, 8·68% H, 4·81% N.

N-(6,7-Oxido-3,7-dimethyloctyl)-*p*-aminoacetophenone (*IV*)

3 ml of 0·9M ether solution of perphthalic acid was added to a solution of 0·44 g N-trifluoroacetyl-N-(3,7-dimethyl-6-octenyl)-*p*-aminoacetophenone (1·19 mmol) in 5 ml ether and the mixture was left to stand at room temperature for 24 h. After the same treatment as with derivative *III*, product *IV* was obtained in a 72% yield. The mass spectrum showed peaks at *m/e* 289 (M), 274, 273, 203, 189, 148. For analytical purposes the sample was distilled at 0·01 Torr and a bath temperature 230°C. For $C_{18}H_{27}NO_2$ (289·4) calculated: 74·69% C, 9·40% H, 4·84% N; found: 74·62% C, 9·58% H, 5·08% N.

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