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IDENTIFICATION OF HETEROCYCLIC PRODUCTS ORIGINATING FROM ATTEMPTS TO SYNTHESIZE 3-FLUORO--8-TRIFLUOROMETHYLDIBENZO(b,f)THIEPIN-10(11H)-ONE

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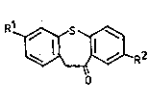
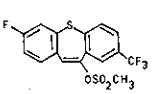
The title ketone I was an intermediate in the synthesis of potential neuroleptics. Attempts at its preparation by cyclization of 4-fluoro-2-(4-trifluoromethylphenylthio)phenylacetic acid (II) with polyphosphoric acid, polyphosphoric ester or anhydrous H_2F_2 proceeded with very low yields (10%; in the first case, the keto acid III was the main product). Cyclization with methanesulfonic acid and P_2O_5 in chlorobenzene afforded in addition to the enol sulfoester IV a substance $C_{21}H_9ClF_4OS$, assumed to be a substituted tribenzo(b,e,h)furo(2,3-d)thiepin. Chlorobenzene, probably oxidized in small extent with air oxygen to 4-chlorophenol, participated evidently in its formation.





IV

I, $R^1 = F$, $R^2 = CF_3$
III, $R^1 = F$, $R^2 = COOH$
VII, $R^1 = OCH_3$, $R^2 = CF_3$

Compound IV yielded by hydrolysis with a solution of NaOH in aqueous ethanol the desired ketone I. Carrying out the cyclization in 1,1,2,2-tetrachloroethane resulted in a high yield of the sulfoester IV and opened a preparative access to the ketone I. In one experiment, a compound $C_{16}H_{11}F_3O_2S$ resulted as the final product of the whole sequence and was identified as 6-ethoxy-2-trifluoromethylthioxanthone; its formation is explained by oxidation of ketone I to the α-diketone, following benzilic rearrangement, decomposition of the formed α-hydroxy acid and the final nucleofilic substitution of the activated fluorine atom.

Further heterocyclic compounds were obtained in various synthetic approaches to the starting acid II. In an attempt at elimination of the amino groups from bis(2-amino-4-trifluoromethylphenyl) disulfide, containing the corresponding sulfide as a contaminant, 5-trifluoromethyl-1,2,3-thiadiazole was the main product and 2,8-bis(trifluoromethyl)phenothiazine a minor one. A reaction of the Zn salt of 2-amino-4-trifluoromethylthiophenol with 4-fluoro-2-iodophenylacetic acid gave in addition to the desired 2-(2-amino-4-trifluoromethylphenylthio)-4-fluorophenylacetic acid (V) an acid $C_{22}H_{14}F_4N_2O_2S_2$, identified as a derivative of the benzothiazole-5-carboxylic acid. Deamination of acid V to acid II was accompanied by formation of 1-fluoro--8-trifluoromethyldibenzothiophene-4-acetic acid and its ethyl ester. Finally, in the synthesis of 4-fluoro-2-(4-trifluoromethyl-2--nitrophenylthio)phenylacetic acid (VI) by reaction of 6-fluorobenzo(b)thiophen-2(3H)-one with 4-chloro-3-nitrobenzotrifluoride in aqueous ethanol in the presence of K_2CO_3 and KI, a small amount of compound $C_{23}H_{12}F_5NO_4S_2$ was formed, which was identified as the fixed enol form of a product of acylation of the starting thiolactone with the formed acid VI or with its activated ester.

Dieckmann cyclization of methyl 4-fluoro-2-(4-trifluoromethyl--2-methoxycarbonylphenylthio)phenylacetate by means of potassium tert. butoxide in xylene gave evidently the enol form of the expected keto ester which, however, underwent transesterification under formation of a heptacyclic dilactone, derivative of tetrabenzo(a,d,j,m)dithiepino(4,5-b;4',5'-f)-1,5-dioxocin-11,22-dione. The formed methanol was able to effect in a small amount of the product a nucleofilic substitution of the fluorine atome resulting in 8-trifluoromethyl-3-methoxydibenzo(b,f)thiepin-10(11H)-one.

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SYNTHESES OF 6H-DIBENZ(b,e)-1,4-OXATHIEPIN AND 11H-DIBENZ(b,f)-1,4-OXATHIEPIN DERIVATIVES

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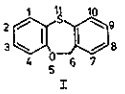
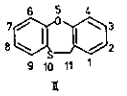
Reaction of 2-iodobenzoic with 2-methoxythiophenol gave 2--(2-methoxyphenylthio)benzoic acid which was reduced to 2--(2-methoxyphenylthio)benzyl alcohol. The following treatment with hydrogen bromide afforded 2-(2-methoxyphenylthio)benzyl bromide which was demethylated; the best agent for this purpose was found in boron tribromide. The resulting 2-(2-hydroxyphenylthio)benzyl bromide was not isolated but immediately cyclized with sodium hydroxide in aqueous dimethyl sulfoxide to give 6H-dibenz(b,e)-1,4-oxathiepin (I).



I



II

Efforts to use this system in the preparation of pharmacologically interesting substances led to attempts at a functionalization of the 6-position. Treatment with N-bromosuccinimide, giving in the case of isochroman the corresponding 1-bromo derivative, gave in our case 2-bromo-6H-dibenz(b,e)-1,4-oxathiepin. Likewise a reaction with chlorine at low temperatures yielded only the 2-chloro derivative. A further action of chlorine on this product and the following hydrolysis led to the corresponding sulfoxide. It was thus necessary to find another method of synthesis of the 6-substituted compounds. The dimethylamide, prepared from 2-(2-methoxyphenylthio)benzoic acid, was reduced with lithiumtriethoxyaluminium hydride to 2-(2-methoxyphenylthio)benzoldehyde which was treated with sodium hydroxide in chloroform in the presence of triethylbenzylammonium chloride as a phase transfer catalyst which resulted in 2-chloro-2-[2-(2--methoxyphenylthio)phenyl] acetic acid. Demethylation with boron tribromide and the following cyclization with sodium hydroxide in dimethyl sulfoxide gave a tediously separable mixture of 6H-dibenz(b,e)-1,4-oxathiepin-6-carboxylic acid and its 2--bromo derivative. For preventing the bromination in the very reactive position 2 of the skeleton, this position was blocked by substitution with fluorine. The known 4-fluoro-2-methoxyaniline was transormed by the xanthate method to 5-fluoro-2--methoxythiophenol which was condensed with 2-chlorobenzaldehyde in hexamethylphosphoric triamide and afforded 2-(5--fluoro-2-methoxyphenylthio)benzaldehyde. An analogous sequence of reactions as in the non-fluorinated series resulted then in 2-fluoro-6H-dibenz(b,e)-1,4-oxathiepin-6-carboxylic acid.
The basic representative of the new and isomeric system, 11H--dibenz(b,f)-1,4-oxathiepin (II) was obtained in the following manner: Reaction of 2-methoxythiophenol with 2-bromobenzyl bromide yielded 2-methoxyphenyl 2'-bromobenzyl sulfide which was demethylated with hydrogen bromide to 2-hydroxyphenyl 2'-bromobenzyl sulfide. Cyclization of this compound in dimethylformamide in the presence of pottassium carbonate and copper afforded the desired substance II. The structures all products were carroborated by analyses and spectra.