INVESTIGATION OF PATHS FOR
THE SYNTHESIS OF 5,5-DIALKYL-
3-PERFLUOROALKYL-5,6-DIHYDRO-
1,2,4-TRIAZOLO[3,4-a]ISOQUINOLINES

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Substituted 3-trifluoromethyl-5,6-dihydro-1,2,4-triazolo[3,4-a]isoquinolines were obtained by the reaction of substituted 1-methylthio-3,4-dihydroisoquinolines with hydrazine hydrate and trifluoroacetic acid. The corresponding 3-perfluoroalkyl derivatives are formed in the course of dehydration of 2-(3,3-dimethyl-3,4-dihydro-1-isouquinolyl)hydrazides of perfluorocarboxylic acids.

Keywords: hydrazides, hydrazones, isoquinoline, 1,2,4-triazolo[3,4-a]isoquinoline, perfluorocarboxylic acids, perfluorocarboxylic esters.

The condensed derivatives of quinoline and isoquinoline substituted by perfluoroalkyl groups are extremely promising for the creation of new biologically active compounds [1, 2]. Earlier we described a method for the synthesis of 3-methyl- and 3-aryl-1,2,4-triazolo[3,4-a]isoquinolines [3]. In the present paper we consider methods for the production of triazolo[3,4-a]isoquinolines (la-e) containing perfluoroalkyl group CF,CF-CF,CF,-, where n = 0, 1, or 2, at position 3. The compounds are of interest as they are isosteres of 1,2,4-triazolo[3,4-a]-phthalazines – well-known agonists of benzodiazepine receptors [4]. To compare the physicochemical characteristics we also synthesized triazolo[3,4-a]isoquinolines (lf,g) unsubstituted at position 3 and also the 3-alkyl-substituted derivatives (lh,i) (Scheme).

The reaction of heterocyclic hydrazines with carboxylic acids or their derivatives is a classical method for the production of condensed triazolo-heteroarenes [5]. Heating of amidrazones in carboxylic acids (method A) leads smoothly to triazolo[3,4-a]isoquinolines for acetic, propionic, and trifluoroacetic acids (see Table 1; compound lh was described earlier [3]). Since thiorethers 2a,b are known to react readily with amines in acetic acid [6], we also developed an one-pot method for the production of compounds 1a,b,h by the direct reaction of thiorethers 1a,b, hydrazine hydrate, and the respective acid with boiling (method B); compounds 1a,b,h are obtained here in a fairly pure state but with smaller yields (Table 1).

It could be expected that the reaction of amidrazones 3a,b with formic acid would take place smoothly and lead to compounds 1f,g. However, the reaction of 99% formic acid with compound 3a both at room temperature and with boiling (1-5 h) leads to oligomeric products and to the previously described [7] azine of 3,3-dimethyl-3,4-dihydroisocarbostyril (4). In this case heterocyclic hydrazones clearly disproportionate to azine and hydrazine hydrate under the influence of formic acid, as is possible for this type of compounds [5]. We tried to produce compound 1f through thioether 1a and formylhydrazine, but the reaction of these substances in boiling methanol again gives mainly azine 4, while increase in temperature (reaction in boiling o-dichlorobenzene) leads as could be expected to self-condensation of formylhydrazine and gives a moderate yield (30%) of compound 4a. The latter was obtained by an alternative method with a yield of 90% by boiling this ether 1a and 4-amino-1,2,4-triazole for 2 h in glacial acetic acid.

An attempt to bring formic acid into the reaction under the conditions of method A led to a mixture of polymeric and oligomeric products, compound 1f, and the corresponding dimer bis-1,4-(3,3-dimethyl-3,4-dihydro-1-isoquinolyl)-1,2,4,5-tetrahydrotetrazine (5), which could not be isolated in the pure form. The dimer 5 was identified by its mass spectrum (M+ 398) as an impurity in insufficiently purified samples of compound 1f. The formation of such a dimer was described earlier for the reaction of orthoformic ester with phenylhydrazine hydrochloride [8]. The reason for the anomalous behavior of formic acid with amidrazones 3a,b is evidently connected, on the one hand, with its increased acidity (compared with acetic acid) and, on the other, with the bifunctionality and dual reactivity.

Unlike formic acid itself, its derivatives react with amidrazones 3a,b without anomalies. Thus, the boiling of amidrazones 3a,b for 1-2 h in an excess of ethyl orthoformate (method C) leads to triazololo[3,4-a]isoquinolines (1l,g) not substituted at C-3 (Table 1). The exothermic reaction of amidrazone 3a with the mixed anhydride of formic and acetic acids according to the method [3] leads to the same result.

An attempt to extend method B to perfluoropropanoic acid gave a mixture of hydrazides 6b,c and the target triazololo[3,4-a]isoquinolines 1b,c in a ratio of ~2:1 (according to the 1H NMR spectra). To obtain compounds 6b,c in the pure form we used the reaction of hydrazones 2a,b with methyl esters of perfluorocarboxylic acids, since the latter is known to react readily with amines even at room temperature [9]. In fact, the reaction of methyl perfluoropropionate with amidrazones 3a,b (toluene, 20°C, 12 h) gives pure hydrazides 6b,c, which undergo cyclization to compounds 1c,d when boiled in acetic anhydride (method D).

Methyl perfluorobutyrate reacts with amidrazones 3a,b in a similar way, but the further dehydration of the obtained hydrazides 6d,e by the action of acetic anhydride is no longer possible and only takes place with phosphorus pentoxide (method E). Published data [10] indicate that with increase in the size of the perfluoroalkyl radical to C,F, or larger radicals compounds 6d,e can exist in the cyclic form (see the Scheme). The IR and NMR spectra of compounds 6a-f were recorded in order to investigate this question.