Thiazole Derivatives as Potential Chemotherapeutic Agents: Homolytic Arylation of Thiazole with Phenylazotriphenylmethane

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Abstract □ The homolytic arylation of thiazole with phenylazotriphenylmethane (as a free radical source) was carried out to explore the potential chemotherapeutic activity of the resulting triphenylmethyl derivatives. The experimental data differed from similar results on other isosteric heterocycles: one compound only was obtained, having both phenyl and triphenylmethyl groups in the heterocyclic nucleus. The structure of 2-phenyl-5-triphenylmethylthiazole was established by IR, ^{1}H-NMR, and mass spectroscopy. In particular, the mass spectral investigation indicated the cleavage of the 2,3- and 4,5-ring bonds, in contrast with the usual behavior of other thiazole derivatives with no triphenylmethyl substituent.

Keyphrases □ Thiazole—homolytic arylation with phenylazotriphenylmethane, 2-phenyl-5-triphenylmethylthiazole synthesized □ 2-Phenyl-5-triphenylmethylthiazole—synthesized by homolytic arylation of thiazole with phenylazotriphenylmethane □ Arylation, homolytic—thiazole with phenylazotriphenylmethane, 2-phenyl-5-triphenylmethylthiazole synthesized

In the synthesis of thiazole derivatives potentially useful as drugs, research has focused on specifically substituted 2,5-thiazole derivatives. Therapeutic activity related to the thiazole nucleus varies according to both type and position of the substituent; in fact, several derivatives are chemotherapeutic (1–6), hypnotic (7, 8), anesthetic (9, 10), and anti-inflammatory (11) agents.

The chemotherapeutic action is usually related to an electron-withdrawing group on C-5, while the activity is inhibited by introducing a methyl substituent in the 4-position (2). A methyl group on C-4 and an electron-donor group on C-5 promote either a sedative–hypnotic or anesthetic action[1]. A substituent on C-2 has neither determining nor selective influence on the activity.

The present work investigated the influence of the triphenylmethyl substituent on the potential chemotherapeutic activity of the thiazole nucleus. Homolytic arylation of thiazole with phenylazotriphenylmethane as a free radical source yielded 2-phenyl-5-triphenylmethylthiazole (I). The triphenylmethyl group could be relevant for its electronic characteristics and because of its steric effects. In fact, triphenylmethylpenicillin (14) exhibits high resistance to penicillinase.

From a synthetic standpoint, the preparation of I was compared with the syntheses of other arylating agents (15–20) and isosteric five- and six-membered heterocycles such as furan, thiophene, and pyridine (21–25). The reaction could proceed either by addition of the radical species followed by oxidation of the two dihydro derivative isomers obtained with *o*-chloranil, with furan and thiophene (21, 22), or by addition and spontaneous oxidation, as with pyridine (23–25), whose C-2 and C-5 positions have different electronic densities as in thiazole.

[1] A 4-methyl-5-nitro-substituted derivative is, on the contrary, an antipsychotic agent (12); 2,4-diamino-5-phenylthiazole is an analeptic drug (13).

EXPERIMENTAL

Phenylazotriphenylmethane—The Gomberg reaction (26) with bromotriphenylmethane and phenylhydrazine resulted in an almost quantitative yield of phenylazotriphenylmethane. Although alternative methods were proposed (27–29), this reaction was preferred because of its excellent yield and the easy spontaneous oxidation of the starting hydrazo compound, which prevents the use of oxidative agents.

Decomposition of Phenylazotriphenylmethane in Thiazole—A 0.487-g portion of phenylazotriphenylmethane (100:1) was added to 10 ml of thiazole. The mixture was refluxed for 24 hr at 75°, and the reagent decomposed to give the two radicals (30). The resulting clear solution was allowed to evaporate for several days at room temperature. After complete evaporation of the thiazole, the resulting sticky mixture was washed repeatedly with ether. A slightly soluble, whitish compound was separated, mp 175–180° (yield 15%). Its slight solubility in ether caused some losses; however, any other solvent either led to a less pure product or rapidly dissolved it. A similar procedure, using a smaller amount of thiazole, led to resinous products that were not easily identifiable.

Anal.—Calc. for $C_{28}H_{21}NS$: C, 83.35; H, 5.25; N, 3.47; S, 7.93. Calc. for $C_{28}H_{23}NS$: C, 82.94; H, 5.72; N, 3.45; S, 7.89. Found: C, 82.80; H, 5.29; N, 3.48; S, 7.68.

TLC—A chloroform solution containing 25 mg/ml was prepared. TLC was carried out on silica gel[2] 60 F_{254} plates with chloroform–methanol (9:1 v/v) as the eluent. Only one spot was detected, R_f 0.67.

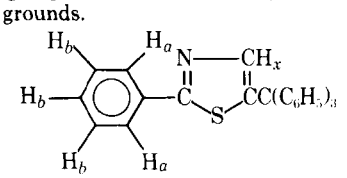
Spectral Data—The IR spectrum[3] was measured as a mineral oil mull. The ^{1}H-NMR spectrum was recorded at room temperature on a spectrometer[4] from a solution in deuterochloroform with tetramethylsilane as the internal standard; chemical shifts are in δ (parts per million). A double-focusing mass spectrometer[5] was used. The most relevant fragments of 2-phenyl-5-triphenylmethylthiazole were: *m/e* 404 (20%), 403 (100), 371 (10), 327 (20), 326 (100), 300 (30), 299 (100), 267 (40), 243 (30), 223 (50), 222 (50), 221 (100), 210 (30), 190 (80), 179 (60), 178 (100), 166 (60), 165 (100), 121 (100), 104 (70), 103 (40), 102 (20), 77 (60), 57 (30), 51 (30), and 45 (30).

RESULTS AND DISCUSSION

Homolytic arylation of the thiazole nucleus gave only one compound, and it contained both phenyl and triphenylmethyl groups. The position of substituents and the type of heterocyclic ring (thiazole or dihydrothiazole) were determined by elemental analysis, TLC behavior, negative reaction with *o*-cloranil, and spectral data.

The IR spectrum was of little diagnostic significance, and the main absorption frequencies (centimeters^{-1}) were assigned by comparison with those of unsubstituted thiazole, phenylazotriphenylmethane, and other arylthiazoles (31): 3042 (ν-CH), 1590 and 1485 (ν-C=N and ν-C=C), 1265–1072 (δ-CH), 760, 752, 740, 700, and 690 (γ-CH) cm^{-1}.

The ^{1}H-NMR spectrum excluded the possibility that the synthesized product was a thiazolidine derivative, all resonance signals falling in the characteristic region of aromatic protons (7.49s, 7.88m, 7.35m, and 7.25s ppm). Furthermore, the presence in the thiazole ring of the phenyl and triphenylmethyl groups, on C-2 and C-5, respectively, was established on the following grounds.



I

[2] Merck.
[3] Perkin-Elmer model 257.
[4] Varian T-60 A (60 MHz).
[5] Varian CH7.

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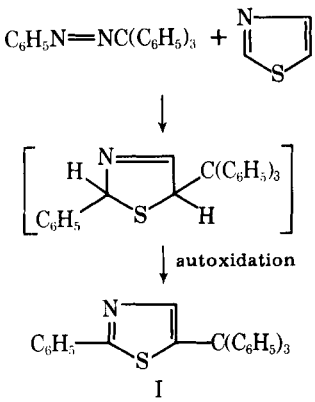


I

Scheme I

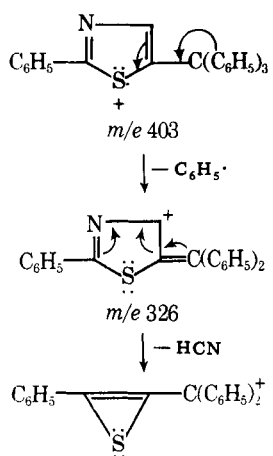
The chemical shift at 7.49 ppm can be attributed to proton H_x on C-4 (I), whereas it is found at 7.86 ppm (31) in the unsubstituted thiazole. If the inductive effects of the electronegative substituents in the ring were considered by themselves, this absorption should take place at lower fields. However, the molecular models show that this proton is shielded by the ring current of a phenyl ring of the triphenylmethyl substituent at C-5, thus shifting to higher fields. If the triphenylmethyl group were in the 4-position, for the same effect, the proton at C-5 could not fall at 7.49 ppm but at a higher value than that found in unsubstituted thiazole, *i.e.*, 7.27 ppm.

The singlet at 7.25 ppm is due to the triphenylmethyl group, not only because a sharp singlet occurs at the same position in bromotriphenylmethane but also because the integrated signal corresponds to the theoretical data.

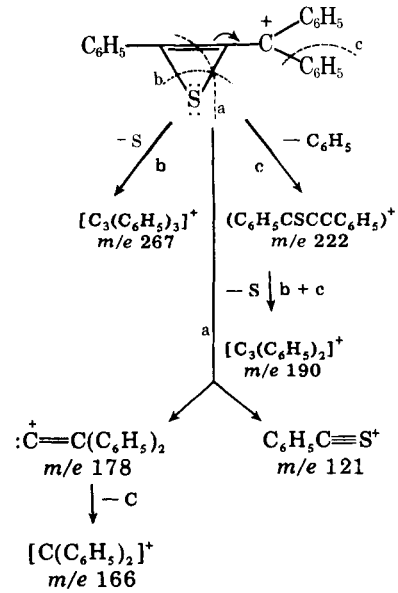
Moreover, the H_a protons of the phenyl group are observed at a lower field (7.88 ppm) than those related to the H_b protons (7.35 ppm). Their different resonances confirm the 2-position for the phenyl substituent; consequently, its *ortho*-protons, in deuterochloroform, are deshielded, as observed (31), on account of the nitrogen anisotropy and of the π-electron deficiency at the 2-position of thiazole. If the phenyl were in the 5-position, its protons should have originated a singlet. On the other hand, this group could not be on C-4 because of steric hindrance of the large triphenylmethyl group on C-5. On these grounds, it was established that the synthesis proceeded according to Scheme I.

Further data from the mass spectral investigation support these conclusions. The peak of the molecular ion is found at *m/e* 403, in agreement with the molecular weight of the phenyltriphenylmethylthiazole, thus excluding a dihydrothiazole derivative.

The base peak at *m/e* 326 corresponds to $(M^+ - C_6H_5\cdot)$: *m/e* 403 − 77. The phenyl radical loss originates from the triphenylmethyl group, no cleavage with loss of a phenyl radical being reported (32) to occur from phenyl-substituted thiazoles. Moreover, this fragmentation mode is confirmed by the *m/e* 210 $[SCC(C_6H_5)_2]^+$, 178 $[CC(C_6H_5)_2]^+$, 121 $(C_6H_5CS)^+$, and 103 $(C_6H_5CN)^+$ peaks. The first ones arise from phenyl radical loss from the triphenylmethyl group; the latter peaks confirm that



Scheme II



Scheme III

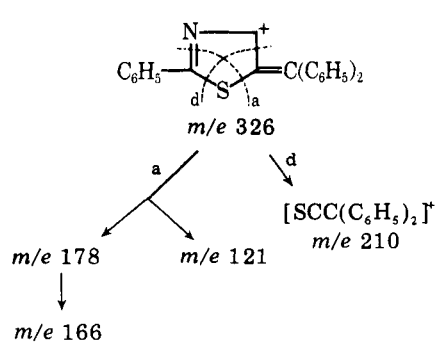
a phenyl radical is still bound to the thiazole C-2 (between N and S), according to previous reports (32) dealing with 2-phenylthiazoles.

To establish the true position of the triphenylmethyl group, the $(M^+ - C_6H_5 - HCN)^+$ peak at *m/e* 299 proved essential. As mentioned previously, when a phenyl substituent is attached to C-2, HCN can never originate from thiazole fragmentation by 1,2- and 3,4-bond cleavage, according to the Clarke *et al.* process (33), as confirmed both on 2-deuterothiazole (34, 35) and on other thiazole derivatives (36, 37). On the contrary, the cleavage of the ring atoms occurred at the 2,3- and 4,5-bond sites, as already established (38) for 2,5-diphenyl-1,3,4-oxadiazole. Therefore, the triphenylmethyl substituent competes with the bond ring cleavage typical of the thiazole nucleus (39). As a consequence, a thiirene derivative at *m/e* 299 is obtained (Scheme II), which allows assignment of the triphenylmethyl group to the 5-position of the thiazole ring, thus confirming the previously assigned structure of the synthesized product.

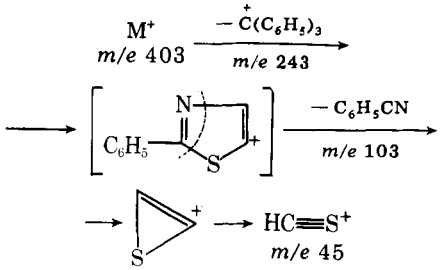
The peaks at *m/e* 121, 178, and 166 are of high intensity and could arise from the thiirene ion (Scheme III) according to pathway a, while peaks at *m/e* 267, 222, and 190 could follow routes b, c, and b + c. The peak at *m/e* 210 $[SCC(C_6H_5)_2]^+$ could also arise from the same thiirene ionic species.

Most of the above fragments could also originate from the $(M - C_6H_5)^+$ ion by an alternative thiazole cleavage according to Scheme IV, a or d, as observed (37) for alkylthiazoles; however, it would then not be possible to explain the peak at *m/e* 299. Therefore, the bond cleavages take place according to Schemes II and III.

Following the observation that the thiazole nucleus fragments in a different manner from the scheme proposed previously (33–37), further investigations were directed to examine whether other peaks could originate by cleavage of the 1,2- and 3,4-ring bonds of the thiazole. The fairly abundant *m/e* 103 peak $(C_6H_5C{\equiv}N)$ confirms such a cleavage. The fragment can originate by preliminary expulsion of the *m/e* 243 $[C(C_6H_5)_3]^+$ followed by the typical cleavage depicted in Scheme V (33), as confirmed by the presence of peaks at *m/e* 57 and 45, usually found



Scheme IV



Scheme V

in thiazole derivatives with electron-withdrawing groups on C-5 or C-2 (36). The two peaks at *m/e* 77 and 51 can be attributed to the $C_6H_5^+$ and $C_4H_3^+$ radical ions.

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Improved Synthesis of *N*-(2,6-Dimethylphenylcarbamoylmethyl)iminodiacetic Acid and Analogs

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Abstract □ A new synthesis of *N*-(2,6-dimethylphenylcarbamoylmethyl)iminodiacetic acid directly from nitrilotriacetic acid was developed. Six analogs also were synthesized. Their technetium Tc 99m complexes were prepared and characterized. Electrophoresis and chromatography were used to determine the radiochemical purity of each complex.

Keyphrases □ *N*-(2,6-Dimethylphenylcarbamoylmethyl)iminodiacetic acid—and analogs, synthesized, ^{99m}Tc-complexes prepared □ Technetium Tc 99m complexes—various substituted iminodiacetic acids prepared □ Iminodiacetic acids, substituted—synthesized, ^{99m}Tc-complexes prepared □ Radiopharmaceuticals, potential—^{99m}Tc-complexes of various substituted iminodiacetic acids prepared

In recent years, considerable attention has been given to the development of new γ-emitting radiopharmaceuticals for the evaluation of the hepatobiliary function. Currently, the only commercially available agent of this type is rose bengal sodium I 131 (1). The relatively poor physical characteristics of iodine-131 have hindered the widespread use of this radiopharmaceutical.

DISCUSSION

Because of the nearly ideal physical properties of technetium Tc 99m and its widespread availability in most nuclear medicine laboratories,

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