Preparation and Regiochemical Assignments of New Pyrazolo[3,4-*c*][2,1]benzothiazepines

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The preparation of new pyrazolo[3,4-*c*][2,1]benzothiazepines substituted at the nitrogen atoms of the pyrazole moiety is described. It was carried out by reaction of the 4,9-dihydro-9-methyl-4,10,10-trioxo-1(2)*H*-pyrazolo[3,4-*c*][2,1]benzothiazepine (**1**) with several alkylating agents under both classical and phase-transfer catalysis (PTC) conditions. Assignments of the *N*-alkyl regioisomers obtained were performed by study of their ^{1}H nmr spectra and NOE experiments.

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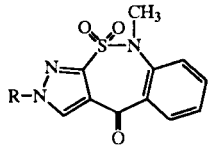
Despite the little biological significance of pyrazole and its reduction products, their participation in chemical structures of important use in human medicine is widely known. The pyrazole nucleus is present in several compounds endowed with hypoglycemic [2], anthelmintic [3], antiandrogen [4], antibacterial [5] and antiemetic [6] activities. It forms part of different molecules in which interesting cardiovascular [7], antineoplastic [8] and antiviral [9] properties have been discovered. Pyrazole rings also constitute fundamental fragments of some compounds which have found utility in the treatment of gout [10], rheumatic disease [11] and other musculoskeletal disorders.

We have synthesized a number of new pyrazole-containing derivatives [12] and some of them were demonstrated to possess noteworthy activities mainly in the psychotropic and nonsteroidal anti-inflammatory fields; those belonging to the 1*H*- and 2*H*-pyrazolo[3,4-*c*][2,1]benzothiazepine ring systems exhibited the most promising activities in their evaluation as antidepressant agents. The synthetic approach for these latter derivatives involved the previous formation of tricyclic intermediate ketones **1** and **2a** in five steps, starting from ethyl 3(5)-aminopyrazole-4-carboxylate and ethyl 3-amino-1-methylpyrazole-4-carboxylate respectively [13]. This approach, however, could not be used for the synthesis of other projected pyrazolobenzothiazepines substituted at the nitrogen atoms of their pyrazole moiety, due to the difficulties found in the preparation of the required aminopyrazole carboxylates or the lack of reactivity of the available aminoesters in the following step of the synthetic route. It was therefore of interest to attempt the synthesis of the desired pyrazolo[3,4-*c*][2,1]benzothiazepines by direct alkylation of the intermediate synthon **1** and to study the regioisomers produced. The present paper deals with the results obtained in this investigation.

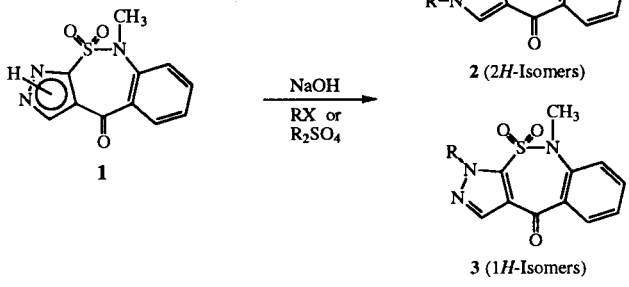


1 R = H
2a R = CH_3

N-alkylation is one of the most important and frequently used reactions of pyrazoles [14]. Despite this, basic aspects of this process such as orientation ratios and mechanism still remain obscure. Elguero [15], in a review of the subject surveying the literature up to 1984, pointed out the lack of empirical rules to predict the orientation of an entering alkyl group on 'unsymmetrical' pyrazoles on the basis of the already existing substituents and reported on the results obtained up to that time. According to these results, alkylation of such 'unsymmetrical' pyrazoles takes place with the preferred formation of the less hindered isomer unless the substituent has a lone pair, for example a carboxyethyl group, whose electrostatic field enhances the nucleophilicity of the adjacent nitrogen atom. Since the publication of this review, most original work in pyrazole alkylation was directed to the search for new methodology, paying less attention to the regioassignments problem [16]. For instance, Begtrup and Larsen [17] performed *N*-alkylation of pyrazoles and other azoles with alkyl halides or dialkyl sulfates under classical conditions but separating deprotonation and nucleophilic displacement steps to allow a better control of the reaction and facilitate the problem-handling of the process. However, the major part of the research carried out in the last ten years was centered on the use of liquid-liquid and solid-liquid phase transfer catalysis (PTC) [18] or, even better, PTC without solvent [19] which provides higher reactivities and permits its use in combination with ultrasound [20] and microwave irradiation [21] techniques.

We first studied the *N*-alkylation of 4,9-dihydro-9-methyl-4,10,10-trioxo-1(2)*H*-pyrazolo[3,4-*c*][2,1] benzothiazepine (**1**) under classical conditions, by treating a solution of this tricyclic ketone in aqueous sodium hydroxide with several alkyl sulfates and alkyl or arylalkyl halides (Scheme 1). In this one-pot process different combinations of alkylation agents, reaction temperatures and reaction times were used, and the products obtained were generally isolated by filtration of the precipitated solids and subsequent purification by column chromatography. Reaction of **1** with either dimethyl sulfate, diethyl sulfate, benzyl bromide or benzyl chloride gave rise to the formation of mixtures of 1*H*- and 2*H*-alkyl or benzyl regioisomers. Their

Scheme 1



relative percentages, calculated from the ^1H nmr spectra of those mixtures (Table1), indicates that, under the reaction conditions, the less hindered isomer is formed preferably as happens in the alkylation of 3(5)nitropyrazole [15]. Reaction of **1** with cyclohexyl or phenethyl bromide and phenethyl chloride under the same conditions did not yield any of the desired *N*-alkyl derivatives.

Regioisomeric assignment of methyl compounds generated by dimethyl sulfate alkylation of **1** was facilitated, since the 2-methyl derivative **2a** had been synthesized previously by an independent route [13]. Structural assignments for ethyl and benzyl derivatives, which could not be obtained by unambiguous synthesis, were made by study of the ^1H nmr spectra of their respective isomeric mixtures (Figure 1).

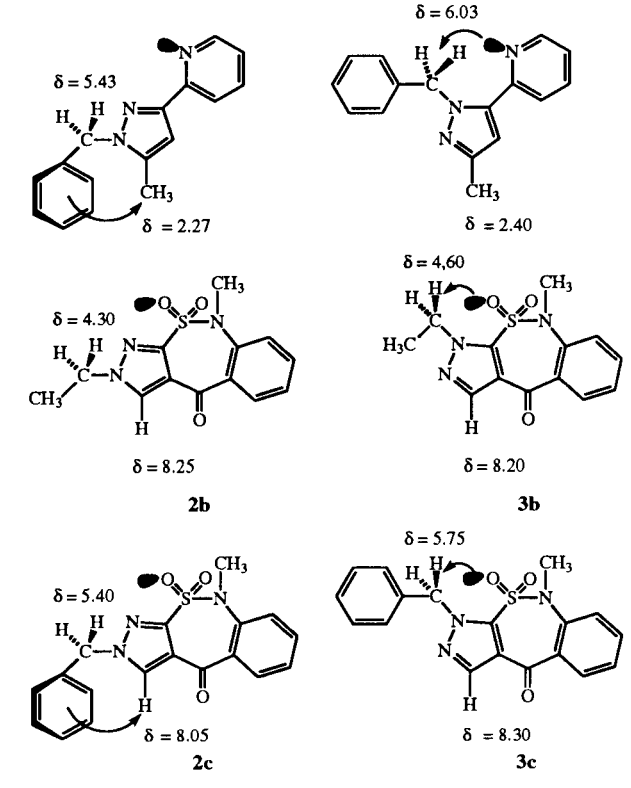


Figure 1

Table 1

Relative Percentages of Regioisomers in the Alkylation of **1**[a]

	Alkylating agent						
	Dimethyl sulfate	Diethyl sulfate	Benzyl bromide	Benzyl chloride	Phenethyl bromide	Phenethyl chloride	Cyclohexyl bromide
Isomer	**a**	**b**	**c**		**d**		**e**
2 (2H)	73	69	90	85	0	0	0
3 (1H)	27	31	10	15	0	0	0

[a] Calculated from ^1H nmr spectra of the regioisomers mixtures. For yields see Experimental.

Thus, for example, the two products obtained in the alkylation of **1** with diethyl sulfate exhibited methylene proton chemical shifts at 4.30 and 4.60 ppm for the major and the minor isomer respectively. We reasoned that this deshielding effect could be explained by the interaction of the lone pairs of the SO_2 group with the adjacent methylene protons, in a similar way to that described for the paramagnetic shift induced by the lone pair of the nitrogen atom in 1-benzyl-3-methyl-5-(2-pyridyl)pyrazole [22]. Consequently, the structure of 4,9-dihydro-2-ethyl-9-methyl-4,10,10-trioxo-2*H*-pyrazolo[3,4-*c*][2,1]benzothiazepine (**2b**) was tentatively assigned to the main regioisomer in the mixture. This assignment was confirmed by experiments of homonuclear NOE difference spectroscopy taking advantage of the possible through-space connection between the proton of the pyrazole ring and the ethyl group methylene protons in the 2*H* regioisomer which, evidently, would be impossible in the case of the 1*H* isomer. NOE experiments were used by Holzer [16] to differentiate isomeric pairs of several substituted pyrazoles. As expected, upon irradiation of the pyrazole proton signal of the first compound the quartet methylene signal gave a strong NOE. Conversely, irradiation at the CH_2 resonance led to a strong enhancement not only of the pyrazole CH singlet but also of the CH_3 signal.

In analogous manner, regioassignments of benzyl derivatives were obtained from the observation of the pyrazole H-3 and benzyl methylene protons signals of both isomers (Figure 1). In fact, the H-3 signal of the most abundant product is shifted upfield as compared to the corresponding H-3 signal in the minor compound due to the

anisotropy of the neighboring benzyl group aromatic ring, thus clearly indicating structure **2c** for this isomer. In contrast, the methylene protons of the minor compound show a downfield shift caused by their proximity to the lone pairs of the sulfonyl group and, therefore, the structure of the 1*H* isomer **3c** was assigned to it.

As it was pointed out, phase-transfer catalysis (PTC) has been successfully employed in the alkylation of pyrazole [18,22,23] and is considered, at present, the method of choice in the synthesis of these compounds. For that reason, we also applied this technique to the synthesis of the above *N*-alkyl derivatives of **1**. Typically, the experiments were carried out by heating at reflux temperature **1** and the alkylating agent in a mixture of 25% aqueous sodium hydroxide and toluene with triethylbenzylammonium bromide (TEBA Br), tetrabutylammonium bromide (TBAB) or tetrabutylammonium hydrogensulfate (TBAS) as the catalysts. The results are summarized in Table 2.

Table 2

Yields (%) of the products isolated from PTC alkylation of **1**

	Alkylating agent							
	Dimethyl sulfate		Diethyl sulfate	Benzyl bromide	Benzyl chloride	Phenethyl bromide	Phenethyl chloride	Cyclohexyl bromide
$Q^+ X^-$	**2a**	**3a**	**2b**	**2c**	**2d**			**2e**
TEBA Br	47	25	44	82	80	68	43	0
TBAB	46	14	56	87	89	70	44	10
TBAS	61	10	64	97	97	73	45	3

Under these conditions, methylation of **1** with dimethyl sulfate produced, independently of the catalyst employed, the methyl regioisomers **2a** and **3a** in a similar way to that described for the alkylation of other unsymmetrical pyrazoles. However, in the rest of the alkylations only one of the two possible *N*-alkyl isomers was obtained. Although each of the three catalysts used in these reactions was effective, tetrabutylammonium hydrogensulfate (TBAS) [24] generally provided the best results.

As mentioned above, the structural assignments in the classical methylation, ethylation and benzylation of **1** were made by comparison between the respective pairs of alkyl isomers 1*H* and 2*H*. In this manner the 2*H* structure was assigned to compounds **2a**, **2b**, and **2c**, and the 1*H* structure to **3a**, **3b**, and **3c**. From this comparison the structures of **2b** and **2c** were also assigned to the compounds obtained by PTC ethylation and benzylation of **1**.

This procedure, however, could not be utilized for the regioassignments of the products isolated from the PTC alkylation of **1** with phenethyl bromide or chloride or cyclohexyl bromide and, therefore, NOE experiments were again employed. Thus, for instance, by irradiating the pyrazole hydrogen of the phenethyl derivative (Figures 2 and 3) an enhancement in the proton signals of the methylene group attached to the pyrazole nitrogen atom was observed. Likewise, irradiation of the signals of these methylene protons produced an enhancement of the H-3 pyrazole signal. This clearly indicated that the phenethyl side chain is in a position adjacent to that of the pyrazole proton and, consequently, the 4,9-dihydro-2-(2-phenylethyl)-9-methyl-4,10,10-trioxo-2*H*-pyrazolo-[3,4-*c*][2,1]benzothiazepine structure (**2d**) was assigned to this compound. A similar NOE study on the compound from the reaction of **1** with cyclohexyl bromide, permitted its characterization as the 2*H* cyclohexyl regioisomer **2e**.

The poor yield of the latter alkylation (Table 2) can be attributed to a competitive β-elimination reaction promoted by the ammonium salts used as catalysts since it is known that secondary substrates, and especially cyclohexyl halides, usually give considerable amounts of alkenes under these conditions [25] This side reaction can also explain the yield differences found for **2d** depending on the phenethyl halide utilized in the alkylation, since it seems clear that there is a greater participation of this elimination reaction in the case of phenethyl chloride relative to the bromide.

In summary, we have demonstrated that phase-transfer catalysis constitutes a simple, effective and selective method for the *N*-alkylation of 4,9-dihydro-9-methyl-4,10,10-trioxo-1*H*-pyrazolo[3,4-*c*][2,1]benzothiazepine (**1**). Consequently, we have been able to assign the regiochemistry of the new benzothiazepines on the basis of both chemical shifts differences and NOE experiments. Benzothiazepines **2** and **3** should serve as precursors to a variety of tricyclic compounds which were designed as potential antidepressant agents.

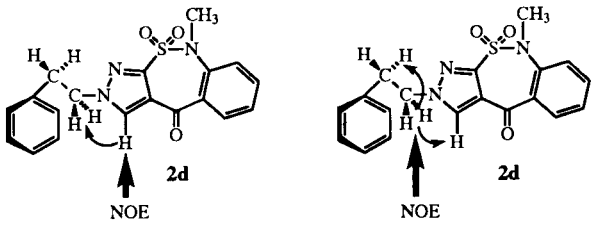


Figure 2

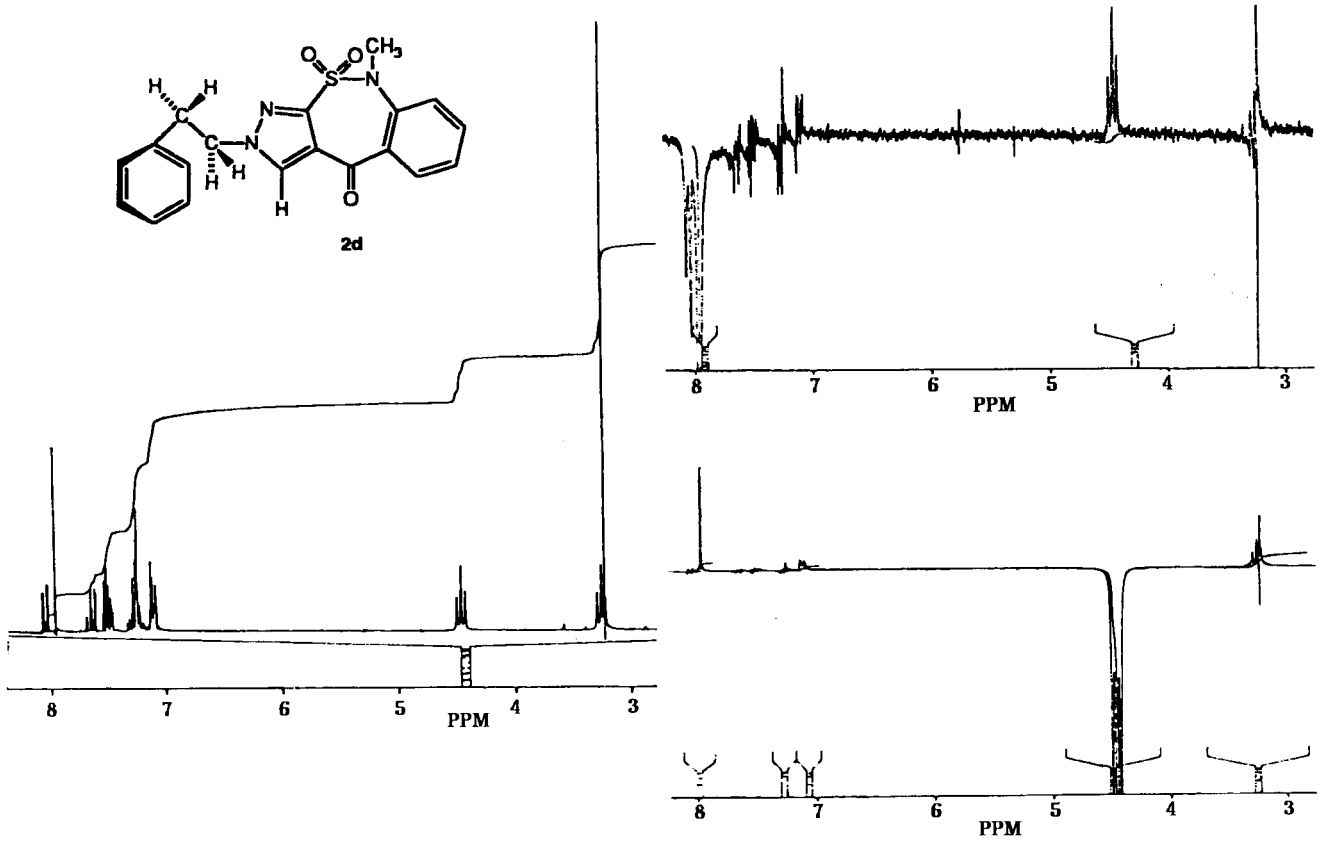


Figure 3

EXPERIMENTAL

Melting points were determined on Gallenkamp capillary apparatus and are uncorrected. ir spectra were recorded using a Shimadzu IR-435 instrument. The ^1H nmr spectra were measured with a Bruker AM-200 and a Varian XL-300 spectrometer. Chemical shift values are reported relative to tetramethylsilane (TMS) in appropriate solvents. The purity of compounds was verified by thin-layer chromatography (tlc) which was run on silica gel GF_{254} (E. Merck) with cyclohexane-ethyl acetate mixtures (2:1 and 1:1 v/v respectively) as eluents. Medium-pressure chromatography was performed using 230-400 mesh silica gel purchased from E. Merck, Inc. Microanalysis were performed at the Centro Nacional de Química Orgánica on a Perkin-Elmer 2400 CHN analyzer.

Alkylation of **1** under Classical Conditions.

General Procedure.

To a solution of 1 (1.32 g, 5 mmoles) in 1*N* sodium hydroxide solution (25 ml), was added dropwise the alkylating agent (5 mmoles). The mixture was stirred for the time and at the temperature indicated below. The precipitated solid was filtered off washed with water and dried. The resulting mixture of the 1*H* and 2*H* regioisomers were separated by column chromatography using a mixture of cyclohexane-ethyl acetate (1:1 v/v) as the eluent and 230-400 mesh silica gel.

4,9-Dihydro-1,9-dimethyl-4,10,10-trioxo-1*H*-pyrazolo[3,4-*c*][2,1]-benzothiazepine **3a**.

After addition of dimethyl sulfate (0.63 g, 0.5 ml) the reaction mixture was stirred for 2 hours at room temperature, giving a solid (0.90 g, 65%) which is the isomeric mixture. By column chromatography the higher R_f isomer was isolated as a white crystalline solid (0.21 g, 15%) of mp 175-177° (ethanol); ir (potassium bromide): 1635 (CO), 1345 and 1160 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.25 (s, 3 H, CH_3), 4.20 (s, 3 H, CH_3), 7.35-7.70 (m, 3 H, phenyl protons), 8.00 (m, 1 H, phenyl protons), 8.15 (s, 1 H, pyrazole).

Anal. Calcd. for $C_{12}H_{11}N_3O_3S$: C, 51.98; H, 3.97; N, 15.16; S, 11.55. Found: C. 51.78; H, 4.05; N, 15.41; S, 11.38.

4,9-Dihydro-2,9-dimethyl-4,10,10-trioxo-2*H*-pyrazolo[3,4-*c*]-[2,1]benzothiazepine **2a**.

Elution of the lower R_f product from the above isomeric mixture gave a white solid (0.64 g, 71%) with mp 203-205° and analytical and spectroscopic characteristics identical to those described for the regioisomer **2a** prepared previously by unequivocal synthesis [12].

4,9-Dihydro-1-ethyl-9-methyl-4,10,10-trioxo-1*H*-pyrazolo[3,4-*c*]-[2,1]benzothiazepine. **3b**.

After addition of diethyl sulfate (0.75 g, 0.65 ml), the reaction mixture was stirred for 2 hours at room temperature giving a mixture of *N*-ethyl isomers (0.56 g, 38%) . By column chromatography the higher R_f isomer was isolated as a white crystalline solid (0.17 g, 12%) of mp. 98-100° (ethanol); ir (potassium bromide): 1635 (CO), 1350 and 1190 (SO_2) cm^{-1}; ^1H nmr

(deuteriochloroform): δ.55 (t, J = 7.5, 3 H, CH_3), 3.30 (s, 3 H, CH_3), 4.60 (q, 2 H, J = 7.5 Hz, CH_2), 7.45-7.80 (m, 3 H, phenyl protons), 8.05 (dd, J_m = 1.5 Hz, J_o = 9.0 Hz, 1 H, phenyl protons), 8.20 (s, 1 H, pyrazole).

Anal. Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.59; H, 4.50; N, 14.42; S, 11.01. Found: C, 53.80; H, 4.80; N, 14.25; S. 10.92.

4,9-Dihydro-2-ethyl-9-methyl-4,10,10-trioxo-2*H*-pyrazolo-[3,4-*c*][2,1]benzothiazepine **2b**.

Elution of the lower R_f product afforded a white solid (0.30 g, 21%) of mp 174-175° (ethyl acetate); ir (potassium bromide): 1635 (CO), 1350 and 1155 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.55 (t, J = 7.5 Hz, 3 H, CH_3), 3.20 (s, 3 H, CH_3), 4.30 (q, J = 7.5 Hz, 2 H, CH_2), 7.30-7.80 (m, 3 H, phenyl protons), 8.10 (dd, J_m = 1.5 Hz, J_o = 9.0 Hz, 1 H, phenyl protons) 8.25 (s, 1 H, pyrazole).

Anal: Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.59; H, 4.50; N, 14.42; S, 11.01. Found: C, 53.70; H, 4.30; N, 14.65; S. 11.38.

1-Benzyl-4,9-dihydro-9-methyl-4,10,10-trioxo-1*H*-pyrazolo-[3,4-*c*][2,1]benzothiazepine **3c**.

(a) With Benzyl Bromide.

After addition of benzyl bromide (0.86 g, 0.6 ml), the reaction mixture was heated at reflux temperature for 1 hour, yielding the isomeric mixture (0.92 g, 52%). By column chromatography the higher R_f isomer was isolated as a white crystalline solid (0.09 g, 5%) of mp 130-132° (ethanol); ir (potassium bromide): 1640 (CO), 1350 and 1155 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.25 (s, 3 H, CH_3), 5.75 (s, 2 H, CH_2), 7.25-8.20 (m, 9 H, phenyl protons), 8.30 (s, 1 H, pyrazole).

Anal. Calcd. for $C_{18}H_{15}N_3O_3S$: C, 61.17; H, 4.28; N, 11.89; S, 9.07. Found: C, 61.23; H, 3.98; N, 12.24; S, 9.05.

2-Benzyl-4,9-dihydro-9-methyl-4,10,10-trioxo-2*H*-pyrazolo-[3,4-*c*][2,1]benzothiazepine **2c**.

Elution of the lower R_f product of the isomeric mixture obtained above afforded a white solid (0.80 g, 45%) of mp 173-175° (ethyl acetate); ir (potassium bromide): 1640 (CO), 1345 and 1155 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.20 (s, 3 H, CH_3), 5.40 (s, 2 H, CH_2), 7.35 (s, 5 H, phenyl protons), 7.40-7.70 (m, 3 H, phenyl protons), 8.00 (dd, J_m = 1.5 Hz, J_o = 7.5 Hz, 1 H, phenyl protons), 8.05 (s, 1 H, pyrazole).

Anal. Calcd. for $C_{18}H_{15}N_3O_3S$: C, 61.17; H, 4.28; N, 11.89; S, 9.07. Found: C, 61.34; H, 4.19; N, 11,69; S, 8,75.

(b) With Benzyl Chloride.

A similar reaction of **1** with benzyl chloride (0.63 g, 0.58 ml) yielded the isomeric mixture (0.85 g, 48%) from which **3c** (higher R_f value) (0.12 g, 8%)was isolated by column chromatography. Elution of the lower R_f isomer of the mixture afforded **2c** (0.60 g, 34%).

Alkylation of **1** under Phase-transfer Catalysis.

General Procedure.

To a stirred solution of sodium hydroxide (2.5 g, 62 mmoles) in water (10 ml) was added the compound **1** (1.32 g, 5 mmoles), the desired ammonium salt (Table 2) (0.06 mmole) and the alkylating agent (5 mmoles) dissolved in toluene (25 ml). The mixture was refluxed with vigorous stirring for 24 hours. After cooling the precipitated solids were filtered, washed with water, dried and recrystallized from the appropriate solvents. Yields are listed in Table 2.

Alkylation of **1** with dimethyl sulfate, under these conditions, gave rise to both isomers **2a** and **3a**. Pure **2a** precipitated in the reaction and was separated by filtration and recrystallized, whereas **3a** was obtained by concentration at reduced pressure of the toluenic phase. The akylation of **1**, under the same conditions, with diethyl sulfate, benzyl bromide, benzyl chloride, phenethyl bromide, phenethyl chloride or cyclohexyl bromide only produced the less hindered regioisomers **2b, 2c, 2d** and **2e**.

4.9-Dihydro-2-(2-phenylethyl)-9-methyl-4,10,10-trioxo-2*H*-pyrazolo[3,4-*c*][2,1]benzothiazepine **2d**.

The white crystalline solid had mp 177-180° (ethyl acetate); ir (potassium bromide): 1635 (CO), 1350 and 1155 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3,25 (m, 5 H, CH_2 and CH_3), 4.45 (t, J = 7.5 Hz, 2 H, CH_2), 6.90-7.30 (m, 5 H, phenyl protons), 7.50 (m, 3 H, phenyl protons), 7.95 (s, 1 H, pyrazole), 8.05 (m, 1 H, phenyl protons).

Anal. Calcd. for $C_{19}H_{17}N_3O_3S$: C, 62.11; H, 4.66; N, 11.44; S, 8.73. Found: C, 62.30; H, 4.63; N, 11.35; S, 8.84.

2-Cyclohexyl-4,9-dihydro-9-methyl-4,10,10-trioxo-2*H*-pyrazolo[3,4-*c*][2,1]benzothiazepine **2e**.

The white crystalline solid had mp 185-187° (ethyl acetate); ir (potassium bromide): 1630 (CO), 1360 and 1160 (SO_2) cm^{-1};^1H nmr (deuteriochloroform): δ 0.80-2.40 (m, 10 H, cyclohexane), 3.25 (s, 3 H, CH_3), 4.20 (m, 1 H, cyclohexane), 7.30-7.70 (m, 3 H, phenyl protons), 8.10 (m, 1 H, phenyl protons), 8.25 (s, 1 H, pyrazole).

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REFERENCES AND NOTES

[1] Present address: Synthélabo, S. A. Avda. de la Industria 31, 28100 Alcobendas (Madrid, Spain).

[2a] E. R. Froesch, H. Waldvogel, V. A. Meyer, A. Jakob and A. Labhart, *Mol. Pharmacol*, **3**, 429 (1967); [b] G. C. Gerritsen and W. E. Dulin, *J. Pharmacol. Exp. Ther.*, **150**, 491 (1965); [c] H. Hohn, I. Polacek and E. Schulze, *J. Med. Chem.*, **16**, 1349 (1973); [d] I. Polacek, E. Schulze, H. Burg and J. Quart, *J. Arzneim.-Forsch.*, **24**, 1242 (1974).

[3a] E. F. Elslager, D. F. Worth and J. D. Howells, G. O. 1,816,086 (1969); *Chem. Abstr.*, **71**, 124442f (1969); [b] L. M. Werbel, *Israel J. Chem.*, **14**, 185 (1975); [c] P. B. Hulbert, E. Bueding and P. E. Hartman, *Science*, **186**, 647 (1974).

[4] S. J. Juniewicz, S. J. Hoekstra and B. M. Lemp, *Endocrinology*, **133**, 904 (1993).

[5a] Y. Inamoto, J. Goto, K. Sakane, T. Kaminura and T. Takaya, *J. Antibiot.*, **44**, 507 (1991); [b] R. H. K. Eng, S. M. Smith and C. E. Cherubin, *32nd ICAAC, Abstr.*, 1992, No. 390, 387, 396, 397, 400.

[6a] P. J. Hesketh and D. R. Gandara, *J. Natl Cancer Inst.*, **83**, 613 (1991); [b] D. R. Nelson, and D. R. Thomas, *Biochem. Pharmacol.*, **38**, 1693 (1989); [c] J. Carmichael, B. M. J. Cantwell, C. H. Edwards, B. D. Zussmann, S. Thompson, W. G. Rapeport and A. L. Harris, *Cancer Chemother. Pharmacol.*, **24**, 45 (1989).

[7] M. J. Ashton, A. W. Bridge, R. C. Bush, L. I. Dron, N. W. Harris, G. D. Jones, D. J. Lythgoe, D. Riddell, and C. Smith, *Biorg, Med. Chem. Letters*, **2**, 375 (1992).

[8a] D. B. Capps, J. Dunbar, S. R. Kesten, J. Shillis, L. M. Werbel, J. Plowman and D. L. Ward, *J. Med. Chem.*, **35**, 4770 (1992); [b] P. M. LoRusso, B. J. Foster, T. H. Corbett, R. A. Wiegand, L. Flaherty, B. J. Redman, E. A. Poplin, M. Valdivielso and L. Baker, *Proc. 7th NCI-EORTC Symp. on New Drugs in Cancer Ther.*, Amsterdam, 1992, p 149.

[9] G. A. Bhat and L. B. Townsend, *J. Chem. Soc., Perkin Trans 1*, 2387 (1981); [b] R. J. Suhadolnik, Nucleoside Anitibiotics, Wiley-Interscience, New York, 1970, p 354.

[10] B. G. Hildick and G. Shaw, *J. Chem. Soc. (C)*, 1610 (1971).

[11a] T. Wagner-Jauregg, *Arzneim-Forsch.*, **19**, 1532 (1969); [b] G. Menorzi, L. Mosti, P. Schemone, M. Damico, M. Falciani and W. Filippeli, *Farmaco*, **49**, 115 (1994).

[12a] S. Vega, M. S. Gil, V. Darias, C. C. Sánchez-Mateo, M. J. Oset-Gasque, M. Perramón and M. P. González, *Eur J. Med. Chem.*, **29**, 233 (1994); [b] S. Vega and J.A. Díaz, Spanish Patent, 2,021,548 (1991); *Chem. Abstr.*, **116**, 214543s (1992)); [c] S. Vega, R. Madroñero, J. A. Díaz, F. Junquera, F. J. Alonso, V. Darias, L. Bravo and S. Abdalah, *Eur J. Med. Chem.*, **23**, 329 (1988).

[13] J. A. Díaz and S. Vega, *J. Heterocyclic Chem.*, **31**, 93 (1994).

[14] A. N. Kost and I. I. Grandberg, Advances in Heterocyclic Chemistry, Vol **6**, A. R. Katritzky and A. J. Boulton, eds, Academic Press, New York, 1966, p 347.

[15] J. Elguero, Comprehensive Heterocyclic Chemistry, Vol **5**, K.T. Potts ed, Pergamon Press, Oxford, 1984, p 167.

[16a] W. Holzer, *Tetrahedron*, **47**, 1393 (1991); [b] W. Holzer and G. Seiringer, *J. Heterocyclic Chem.*, **30**, 865 (1993).

[17] M. Begtrup and P. Larsen, *Acta Chem. Scand.*, **44**, 1050 (1990).

[18a] R. M. Claramunt, J. Elguero and R. Garcerán, *Heterocycles*, **23**, 2895 (1985); [b] A. S. Pogosyan, H. S. Attaryan, G. A. Eliazyan and G. V. Asratyan, *Arm. Khim., Zh.*, **38**, 516 (1985); *Chem. Abstr*, **104**, 186361n (1986); [c] G. V. Asratyan, H. S. Attaryan, A. S. Pogosyan, G. A. Eliazyan, E. G. Darbinyan and S. G. Matsoyan, *Zh. Prikl. Khim.*, **59**, 1296 (1986); *Chem. Abstr.*, **106**, 19633k (1986); [d] A. M. Cuadro, M. P. Matia, J. L. García, J. J. Vaquero and J. Alvarez-Builla, *Synth. Commun.*, **21**, 535(1991).

[19a] E. Díez-Barra, A. De la Hoz, A. Sánchez-Migallón and J. Tejeda, *Synth. Commun.*, **20**, 2849 (1990); [b] E. Díez-Barra, A. De la Hoz, A Sánchez-Migallón and J. Tejeda, *Heterocycles*, **34**, 1365 (1992); [c] E. Díez-Barra, A. De la Hoz, A. Loupy and A. Sánchez-Migallón, *Heterocycles*, **38**, 1367 (1994).

[20] A. Díaz Ortiz, E. Díez-Barra, A. De la Hoz and P. Prieto, *Synlett.*, 893, (1992).

[21] G. Bram, A. Loupy and M. Majdoub, *Synth. Commun.*, **20**, 125 (1990).

[22] G. Tarragó, A. Ramdani, J. Elguero, and M. Espada, *J. Heterocyclic Chem.*, **17**, 137 (1980).

[23] H. J. M. Dou and J. Metzger, *Bull. Soc. Chim. France*, 1861 (1976).

[24] M. Makosza and E. Bialeka, *Synth. Commun.*, **6**, 313 (1976).

[25] G. Roblot, G. Meyer, and P. Viout, *Tetrahedron Letters*, 2331 (1975).