Synthesis of Some 2,3-Dihydro-11b*H*-thiazolo[3,2-*d*][1,4]benzoxazepin-5-(6*H*)one Derivatives. A New Heterocyclic Ring System

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Condensation of (*S*)-penicillamine methyl or ethyl ester hydrochloride with salicylaldehyde and its C-5 derivatives, provided the diastereomeric thiazolidine derivatives **1** and **2**. The resulting amino function was acylated to afford the amides **3** and **4**. Cyclization of the latter led to the 2,3-dihydro-11b*H*-thiazolo[3,2-*d*]-[1,4]benzoxazepin-5-(6*H*)ones **5** and **6**. Conformational data for these heterocyclic compounds are discussed.

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Recently, much work has been carried out on the synthesis and characterization of benzodiazepines condensed with 5-membered heterocyclic rings (1-11). Nevertheless, to our knowledge, analogous tricyclic compounds containing the 1,4-benzoxazepine system have not been described. We report here a procedure for the preparation of thiazolo[3,2-*d*][1,4]benzoxazepine derivatives.

The three-step procedure for the synthesis of the title compounds is illustrated in the following scheme:

Condensation of salicylaldehyde (R′ = H) and its C-5 derivatives (R′ = Cl, NO_2) with the methyl ester (12) or ethyl ester of (*S*)-penicillamine hydrochloride in a buffered solution of 95% ethanol yielded a mixture of two diastereomeric thiazolidines **1a-c** and **2a-c**. The ratio of

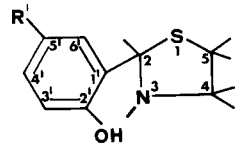

Figure 1. The atom numbering scheme for thiazolidinic derivatives.

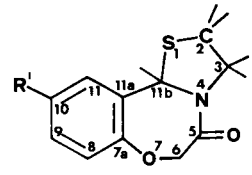

Figure 2. The atom numbering scheme for **5a-c** and **6b,c** derivatives.

SCHEME

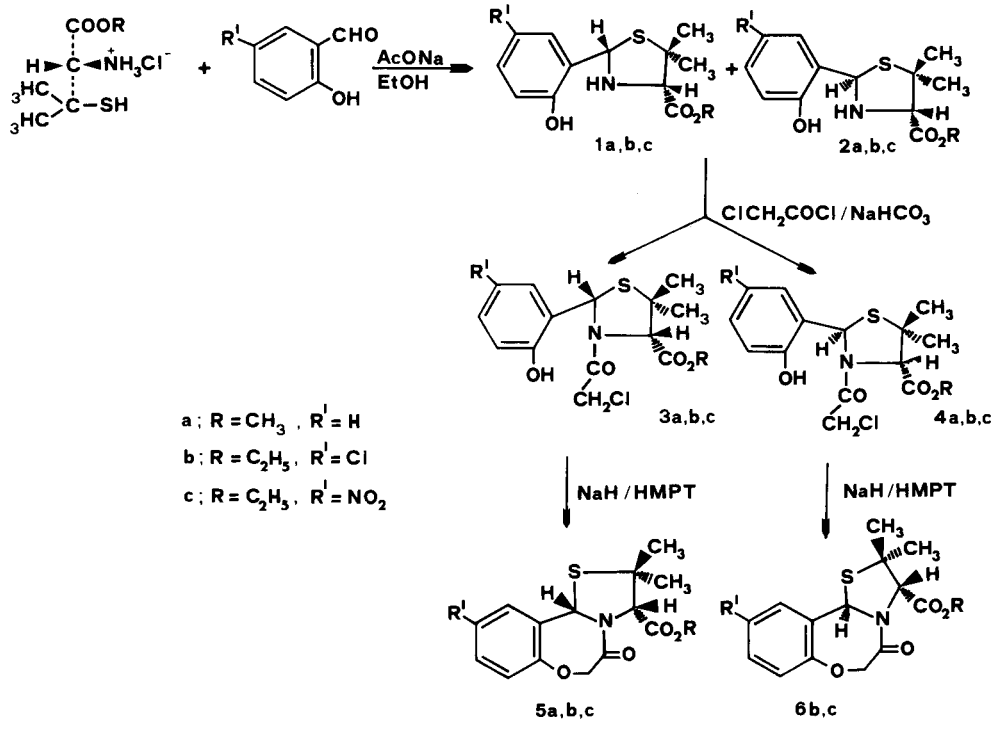

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Table I

Ratios (a), ^{1}H-NMR Data (a), and Elemental Analysis (b) for Diastereomeric 2-(2'-Hydroxyphenyl)-5,5-dimethylthiazolidine Derivatives **1a-c** and **2a-c**

Compound	Ratio (c) 1/2	^{1}H-nmr 2-H (d)	4-H (d)	5-CH_3 (d)		Formula	Analyses % Calcd./Found C	H	N
1a		5.99	3.77 (e)	1.29	1.59				
	1.6					$C_{13}H_{17}NO_3S$	58.40	6.41	5.24
							58.22	6.27	5.26
2a		5.70	3.77 (e)	1.37	1.71				
1b		5.90	3.70	1.29	1.60				
	2.0					$C_{14}H_{18}ClNO_3S$	53.24	5.74	4.43
							53.30	5.79	4.32
2b		5.62	3.76	1.37	1.70				
1c		6.03	3.75	1.36	1.62				
	2.7					$C_{14}H_{18}N_2O_5S$	51.52	5.56	8.58
							51.35	5.66	8.74
2c		5.75	3.90	1.43	1.72				

(a) Our values for **1a** and **2a** are in agreement with those reported by E. Ohler and U. Schmidt, *Chem. Ber.*, **112**, 107 (1979). (b) Performed on samples of unresolvable diastereomeric mixtures. (c) Calculated from 2-H signal intensities. (d) Singlets. (e) A possible $\Delta\delta$ between **1a** and **2a** 4-H signals could not be observed because of overlapping with the -OCH_3 signal.

Table II

Physical and Analytical Data for Diastereomeric 2-(2'-Hydroxyphenyl)-3-Chloroacetyl-5,5-dimethylthiazolidine Derivatives **3a-c** and **4a-c**

Compound	Yield (a) % (3+4)	Ratio 3/4	Mp, °C Crystallization Solvent (b)	$[\alpha]_D$, Solvent (b)	Ms m/e (M^+)	Formula	Analyses % Calcd./Found C	H	N
3a			217-218	−140° (c, 0.8, T)	343	$C_{15}H_{18}ClNO_4S$	52.39	5.28	4.07
	74.6	7.8	M				52.15	5.32	3.93
4a (c)				+243° (c, 1.0, C)	343	$C_{15}H_{18}ClNO_4S$			
3b			188-189	−125° (c, 0.8, T)	391	$C_{16}H_{19}Cl_2NO_4S$	48.98	4.88	3.57
	80.1	1.6	M				49.14	4.93	3.47
4b			150-151	+250° (c, 1.1, C)	391	$C_{16}H_{19}Cl_2NO_4S$	48.98	4.88	3.57
			EA-H				48.96	4.80	3.31
3c			236-237	−142° (c, 0.5, M)	402	$C_{16}H_{19}ClN_2O_6S$	47.70	4.75	6.95
	72.8	0.7	M				47.61	4.88	6.77
4c			184-185	+286° (c, 2.0, C)	402	$C_{16}H_{19}ClN_2O_6S$	47.70	4.75	6.95
			M-LP				47.95	4.78	6.74

(a) Overall yields calculated from weights of pure chromatographic fractions. (b) M = methanol; EA = ethyl acetate; H = hexane; LP = light petroleum; T = tetrahydrofuran; C = chloroform. (c) This product, obtained in low yield, was not further characterized.

these isomers (Table I) was determined by ^{1}H-nmr analysis of the corresponding mixtures measuring the 2-H peak intensities, since in each pair of diastereomers these signals are better separated ($\Delta\delta \cong 0.3$ ppm) than those of the C-4 proton. Conversely, assignment of configuration for **1a-c** and **2a-c** was made on the basis of the chemical shift of the C-4 proton. Following the work of McMillan and Stoodley (13) we have thus assigned the 2*S*,4*S* (*cis*) configuration to the isomer obtained in higher yield, whose proton resonates at the highest field and the 2*R*,4*S* *(trans)* one to the other. Attempts to separate **1a-c** from **2a-c** by column chromatography on silica gel failed, since enriched fractions of *trans* isomers quickly underwent equilibration which led to the same ratio as observed in the starting mixtures. It has been reported that thiazolidine derivatives undergo a similar isomerization (14-16).

Treatment of the mixture of amines **1a-c** and **2a-c** with chloroacetyl chloride in the presence of sodium bicarbonate gave the corresponding *N*-chloroacetyl thiazolidines **3a-c** and **4a-c**, which were separated by column chromatography on silica gel. Their relative ratio, also determined by ^{1}H-nmr analysis before the chromatographic separa-

Table III

Spectral Data for **3a-c** and **4a-c** Derivatives

Compound	^{1}H-NMR (DMSO-d$_6$) 2-H (a)	4-H (a)	5-CH$_3$ (b)		6'-H (a, c)	Other Aromatics	IR, cm^{-1}
3a	6.50 (b)	4.62 (b)	1.26	1.56	8.03 (d)	6.70 - 7.29 (3H, m)	3300, 1742, and 1635
4a	6.50 (e)	4.83 (e)	1.27	1.50		6.65 - 7.38 (4H, m)	3380, 1752, and 1638
3b	6.40 and 6.52	4.63 and 4.89	1.30	1.58	7.88 and 8.17	6.79 - 7.33 (2H, m)	3280, 1740, and 1635
4b	6.30 and 6.49	4.89 and 5.03	1.32	1.55		6.75 - 7.40 (3H, m)	3235, 1708, and 1663
3c	6.40 and 6.56	4.65 and 4.94	1.29	1.59	8.83 and 9.07	7.06 (1H, br d, 3'-H) and 8.13 (1H, br dd, 4'-H)	3300, 1732, and 1645
4c	6.28 and 6.53	4.92 and 5.15	1.33	1.55		7.04 (1H, br d, 3'-H) and 7.90 - 8.27 (2H, br)	3160, 1705, and 1672

(a) For **3b,c** and **4b,c** the presence of two broad signals may be due to *cis-trans* isomerism about the amide C-N bond. (b) Singlets. (c) For **4a-c** this proton is not separated from the other aromatics. (d) Broad doublet. (e) Broad singlet.

Table IV

Physical and Analytical Data for Diastereomeric 2,3-Dihydro-11b*H*-thiazolo[3,2-*d*][1,4]benzoxazepin-5-(6*H*)one Derivatives **5a-c** and **6b,c**.

Compound	Yield %	Mp, °C Crystallization Solvent (a)	$[\alpha]_D$ (b)	Ms m/e (M$^+$)	Formula	Analyses % Calcd./Found C	H	Cl	N	S
5a	62.1 (c)	131-132	+94°	307	$C_{15}H_{17}NO_4S$	58.61	5.57		4.55	10.43
		H				58.56	5.59		4.67	10.58
5b	66.3 (c)	93-93.5	+26°	355	$C_{16}H_{18}ClNO_4S$	54.00	5.09	9.96	3.93	9.01
		EE-H				54.06	5.10	9.90	3.92	9.17
6b	53.1 (c)	132-133	+23°	355	$C_{16}H_{18}ClNO_4S$	54.00	5.09	9.96	3.93	9.01
		M				53.93	5.14	10.06	3.91	8.81
5c	96.0 (d)	119-120	−9°	366	$C_{16}H_{18}N_2O_6S$	52.45	4.95		7.65	8.75
		M				52.30	5.04		7.67	8.74
6c	94.0 (d)	162-163	+100°	366	$C_{16}H_{18}N_2O_6S$	52.45	4.95		7.65	8.75
		M				52.47	5.03		7.56	8.63

(a) H = hexane; EE = ethyl ether; M = methanol. (b) (*c*, 1.0, chloroform). (c) Yield calculated after plc. (d) Yield inferred from weight of crude residue nearly homogeneous on tlc.

tions, did not reflect, particularly in the case of the pairs **3a,4a** and **3c,4c**, the ratio previously determined for the corresponding amines (Tables I and II). As shown in Table II, **3a** was the vastly preferred acylation product, while, surprisingly, the derivative **4c** was the prevailing isomer arising from thiazolidines **1c** and **2c**. The lack of transformation of **3c** to **4c** under the acylation conditions, seems to exclude a thermodynamic control of the distribution of the *N*-chloroacetyl derivatives. It seems thus reasonable to assume that the different acylation rates of the two diastereomeric amines together with a continuous thermodynamic control of their compositions, would lead to the observed product distributions. The higher yield of isomer **4c** compared with **3c** may be rationalized assuming that a strong preferential intramolecular association (hydrogen bond) between the phenolic and amino groups in **1c** inverts the acylation rates observed in the case of 5'-unsubstituted amines **1a** and **2a**. Accordingly, an intermediate behaviour was exhibited by **1b** and **2b** (Tables I and II).

Intramolecular cyclization of pure *N*-chloroacetyl thiazolidines **3a-c** and **4b,c** on treatment with sodium hydride in hexamethylphosphoric triamide (HMPT) at room temperature afforded the expected 2,3-dihydro-2,2-dimethyl-11b*H*-thiazolo[3,2-*d*][1,4]benzoxazepin-5-(6*H*)-ones **5a-c** and **6b,c** in good yields (Table IV) and no isomerization was noted. Evidence for the assigned structures derives from analytical data, molecular weights determined by ms, ir and nmr spectra which are collected in Tables IV and V. A characteristic feature in the ^{1}H-nmr spectra of all 1,4-benzoxazepine derivatives is the presence of a sharp AB quartet (J = 16 Hz) assigned to the -OCH$_2$CO- group. It is noteworthy that, while in (3*S*,11b*S*)-diastereoisomers **5a-c** the signals of two methyl groups at C-2 are well separated ($\Delta\delta > 0.2$ ppm), in the (3*S*, 11b*R*)-derivatives **6b,c** they are superimposed or very close. The

Table V

Spectral Data for **5a-c** and **6b,c** Derivatives

Compound	^{1}H-NMR 2-CH_3 (a)		3-H (a)	6-H_2 (b)	8-H (c)	9-H (d)	11-H (e)	11b-H (a)	Other Signals	Ir, cm^{-1}
5a	1.48	1.73	4.72	4.33 and 4.92				6.66	3.65 (3H, s, -CO_2CH_3), 7.06-7.71 (4H, m, aromatic)	1755 and 1648
5b	1.49	1.70	4.71	4.28 and 4.88	7.06	7.33	7.59	6.57	1.13 (3H, t, -CH_2CH_3), 4.11 (2H, q, -CH_2CH_3)	1740 and 1645
6b	1.51	1.57	4.83	4.34 and 4.91	7.07	7.31	7.79	6.68	1.30 (3H, t, -CH_2CH_3), 4.27 (2H, q, -CH_2CH_3)	1750 and 1645
5c	1.52	1.74	4.75	4.43 and 5.06	7.26	8.29	8.55	6.64	1.13 (3H, t, -CH_2CH_3), 4.12 (2H, q, -CH_2CH_3)	1745 and 1675
6c	1.53 (f)		4.79	4.47 and 5.09	7.23	8.25	8.76	6.74	1.31 (3H, t, -CH_2CH_3), 4.28 (2H, q, -CH_2CH_3)	1750 and 1663

(a) Singlets. (b) A and B of a sharp AB quartet (J = 16 Hz). (c) Doublet (J = 8 Hz). (d) Doublet of doublet (J = 8 and 2.5 Hz). (e) Doublet (J = 2.5 Hz). (f) The two singlets are superimposed.

Table VI

^{13}C-NMR Chemical Shifts, δ, and Multiplicities for Compounds **5c** and **6c**

Compound **5c**	Atom	Compound **6c**
51.2 (s)	C_2	50.4 (s)
31.7 (q)	2β-CH_3	33.0 (q)
24.5 (q)	2α-CH_3	24.2 (q)
72.7 (d)	C_3	73.6 (d)
61.5 (t)	CH_2 (ethyl)	61.7 (t)
14.0 (q)	CH_3 (")	14.2 (q)
166.9 (s), 168.0 (s)	C_5, C=O (ester)	167.6 (s), 168.5 (s)
72.5 (t)	C_6	72.2 (t)
59.2 (d)	C_{11b}	60.9 (d)
161.9 (s)	C_{7a}	161.9 (s)
121.6 (d), 124.0 (d), 126.2 (d)	C_8, C_9, C_{11}	121.9 (d), 124.6 (d), 126.1 (d)
144.4 (s)	C_{10}	144.1 (s)
132.3 (s)	C_{11a}	133.0 (s)

upfield displacement of the lowfield C-2 methyl signal [assigned to β-Me protons, *trans* to the adjacent -CO_2R group (17,18)], in compounds **6b** and **6c**, may be in part due to a long-range shielding by the anisotropic amide carbonyl. A similar but more important magnetic shielding effect has been reported by Bohlmann and Schumann (19) for axial protons of heterocyclic amides.

In order to confirm the absolute configuration and to obtain some conformational information on the diastereomeric tricyclic derivatives **5a-c** and **6b,c**, a study of internal nuclear Overhauser effect (NOE) (17) was undertaken, the experiments being performed on the pair of nitro-derivatives **5c** and **6c**. Irradiation of the high-field (1.52 ppm) methyl peak (2α-Me) in the ^{1}H-nmr spectrum of **5c** results in an about 15% increase in intensity for 3-H signal, whereas no effect was observed for 11b-H. In addition, saturation of the lowfield (1.74 ppm) methyl group (2β-Me) gives a similar positive effect (*ca.* 23%) on 3-H and an integrated intensity increase of about 8% for the 11b-H signal. A parallel irradiation at 1.53 ppm of two superimposed methyl singlets in the ^{1}H-nmr spectrum of derivative **6c** results in an intensity increase of about 28% for 3-H with no detectable effect on 11b-H. It is noteworthy that a significant NOE (*ca.* 15%) was also recorded for the 11-H aromatic signal. These experimental observations confirm the 3*S*,11b*S* configuration previously assigned to **5a-c** compounds, as inferred from the positive NOE on 11b-H occurring after 2β-Me irradiation of the **5c** derivative. Furthermore, an overall analysis of the NOE results seems to indicate that the two diastereomers **5c** and **6c** adopt different conformations in deuteriochloroform solution. In fact, the positive NOE for 3-H and 11b-H in the **5c** derivative necessitates that 11b-H be spatially proximal to 2β-Me and 3-H to both methyl groups. On the other hand, the absence in **6c** of an NOE between both the Me- groups and 11b-H in addition to the significative NOE for 11-H indicate that the 2β-methyl is spatially proximal to 11-H aromatic. As a consequence the conformation of **6c** (as determined from Dreiding models) is more folded than that adopted by **5c**.

The ^{13}C-nmr data of **5c** and **6c** seem to be consistent with the above results regarding the preferred conformation of the two diastereomers in deuteriochloroform solution. The chemical shifts (20-22) listed in Table VI were

assigned by inspection of the noise-decoupled and off-resonance decoupled ^{13}C-nmr spectra on the basis of a comparison of literature δ values for related compounds. The most significant feature is the higher field resonance position for 2β-methyl in **5c** than in **6c** ($\Delta\delta = -1.3$ ppm) probably due to a conformationally induced 1,3-diaxial relationship of this group to 11b-H (23), as previously suggested by NOE. Besides the downfield displacement ($\Delta\delta = 0.8$ ppm) of C-2 carbon in **5c** with respect to the other isomer **6c** may be due to relief of the Pitzer strain to permit an increased staggering of substituents at C-2 and C-3 (21). This is in agreement with the positive NOE found for 3-H after saturation of both 2β and 2α-Me groups. Finally, the downfield position of C-3 and C-11b carbons in **6c** (compared with those in **5c**) could be caused by decrease in electron density (20) of these sites as a result of the predominant contribution of the resonance dipolar form of the amidic group, deriving from an increased planarity of the system. In this connection it is noteworthy that the protons bonded to those two carbons in **6c** resonate downfield compared with those in **5c**.

Therefore an overall analysis of ^{1}H and ^{13}C-nmr data permits us to suggest that in both of the tricyclic diastereomers the C-2 carbon deviates from the best thiazolidine ring plane to the side opposite to the carboxylic group, giving rise to a more puckered molecule for **6c** than **5c**.

The **5a-c** and **6b,c** derivatives were tested for their capability to interfere with both ^{3}H-GABA and ^{3}H-diazepam binding. Only the diastereomer **6c** produces a small decrease (−15%) of ^{3}H-diazepam binding.

EXPERIMENTAL

Melting points were determined with a Büchi oil-bath apparatus and are uncorrected. Optical rotations were taken at room temperature in a 1 dm cell with a Schmidt-Haensch polarimeter. Infrared spectra (potassium bromide) were recorded with Perkin-Elmer 521 and 177 spectrophotometers. ^{1}H-nmr spectra were measured with a Varian EM-390 spectrometer using, unless otherwise specified, deuteriochloroform as the solvent. ^{13}C-nmr spectra were recorded on a Varian CFT-20 spectrometer for solutions in deuteriochloroform. All chemical shifts are reported in δ units, parts per million downfield from internal tetramethylsilane. In the NOE studies, ^{1}H-nmr spectra were recorded with a Varian HA-100 spectrometer by a frequency-sweep method, using a Hewlett-Packard 4204A irradiating audio oscillator. Experimental measurements were carried out with solutions in deuteriochloroform, containing 10% benzene as an internal field frequency lock. The integrated intensity of each peak of interest was measured both before and during irradiation, relatively to signal strengths of closed protons, which cannot be affected by NOE. Mass spectra were obtained with a Hewlett-Packard Model 5982A spectrometer with ionization energy 70 eV. Merck silica gel 60 (230-400 mesh) (1:50) was used for column chromatography; preparative layer chromatography (plc) was carried out with Merck F_{254} silica gel (layers 0.5 mm thick). Light petroleum refers to the 40-60° bp fraction. The drying agent used was sodium sulfate.

General Procedure for the Preparation of Diastereomeric 2(*R*)- and 2(*S*)-(2′-Hydroxyphenyl)-5,5-dimethylthiazolidine-4(*S*)-carboxylate **1a-c** and **2a-c**.

To a solution of salicylaldehyde or its 5-Cl, 5-NO_2-derivative (1 mmole) in 95% ethanol (2.5 ml) (*S*)-penicillamine methyl or ethyl ester hydrochloride (1 mmole) and sodium acetate (2 mmoles) were added. The mixture was stirred at room temperature for 3 hours, the solid residue was filtered off and washed with ethyl acetate. Evaporation of the combined filtrate gave a crude product which was purified on a silica gel column. Elution with methylene chloride gave a mixture of the two diastereomeric thiazolidines **1a** and **2a**, (or **1b** and **2b**, or **1c** and **2c**).

General Procedure for the Synthesis of Diastereomeric 2(*R*)- and 2(*S*)-(2′-Hydroxyphenyl)-3-chloroacetyl-5,5-dimethylthiazolidine-4(*S*)-carboxylate **3a-c** and **4a-c**.

N-Acyl derivatives **3a-c** and **4a-c** were prepared by the usual Schotten-Baumann procedure adding gradually chloroacetyl chloride (3 mmoles) to a stirred mixture of the two appropriate amines (1 mmole) in methylene chloride (2.8 ml), in the presence of an aqueous solution of sodium bicarbonate (6 mmoles). The reaction was allowed to proceed under stirring at room temperature for 1 hour and ethyl acetate was added. The organic layers were washed with water, dried and evaporated to give a residue which was chromatographed on a silica gel column. Elution with methylene chloride afforded the less polar *N*-acyl derivative **3a-c**, while the more polar diastereoisomer **4a-c** was separated using methylene chloride-diethyl ether (95:5) as eluant.

General Procedure for the Cyclization of the *N*-Acyl Derivatives **3a-c** and **4b,c** to the Corresponding 2,3-Dihydro-11b*H*-thiazolo[3,2-*d*][1,4]-benzoxazepin-5-(6*H*)ones **5a-c** and **6b,c**.

To a chilled solution of the suitable *N*-acyl derivative (1 mmole) in dry HMPT (0.8 ml), under nitrogen, sodium hydride (1.1 mmoles; previously washed with hexane to remove mineral oil) was added with stirring over a period of 10 minutes. The mixture was then stirred at room temperature for 24 hours. Partition between water and ethyl acetate gave, after usual work-up, a residue which was purified by plc [diethyl ether-light petroleum (7:3) as eluant], except for the nitro-derivatives **5c** and **6c**, which were directly cristallized.

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