Synthesis of New *s*-Triazolo[4,3-*b*]pyridazines

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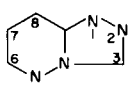
A new synthesis of *s*-triazolo[4,3-*b*]pyridazine derivatives has been achieved starting from 3,6-dichloropyridazine. The method opens the way to substitutions in the 2- or 3- positions. A tricycloderivative, a bis-*s*-triazolopyridazine, has also been synthesized.

The most general methods for the synthesis of *s*-triazolo-[4,3-*b*]pyridazine (I) are represented by the reaction of



I

4-amino-1,2,4-triazole with β-diketones (1-5), or condensation of 3-hydrazinopyridazine with aldehydes (6-12), cyanogen bromide (12-13) or isocyanates (14).

We wish now to report a new and easier synthesis of *s*-triazolo[4,3-*b*]pyridazines starting with 3,6-dichloropyridazine (II).

Treatment of compound II with semicarbazide hydrochloride, followed by refluxing in ethanol containing a small amount of mineral acid gave 6-chloro-2,3-dihydro-*s*-triazolo[4,3-*b*]pyridazine-3-one (III) in good yield.

CHART I

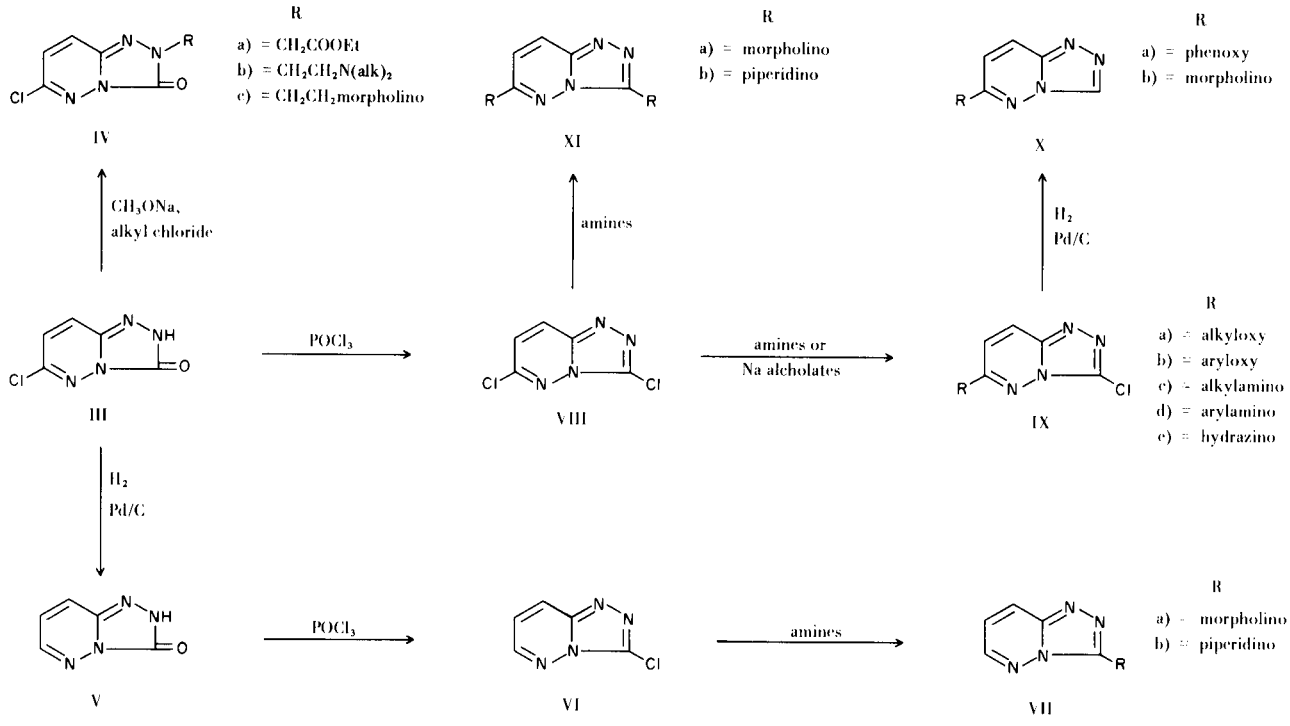
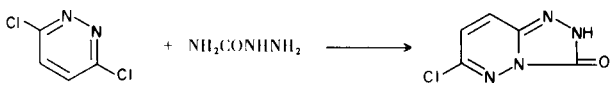


TABLE I

Elemental Analyses

Compound	R	m.p.	Formula	Chlorine, %		Nitrogen, %	
				Calcd.	Found	Calcd.	Found
IV	CH_2CH_2 morpholino	178-179°	$C_{11}H_{14}ClN_5O_2$	12.50	12.70	24.69	24.79
IV	$CH_2COOC_2H_5$	110°	$C_9H_9ClN_4O_3$	13.81	13.84	21.83	22.15
VII	piperidino (a)	124-125°	$C_{10}H_{13}N_5$			34.46	34.00
IX	$NHCH_2CH_2N(C_2H_5)_2$	130°	$C_{11}H_{17}ClN_6$	13.19	13.10	31.27	31.24
IX	$N(CH_2CH_2OH)_2$	169°	$C_{13}H_{20}ClN_5O_2$	11.30	11.37	22.32	22.30
IX	piperidino	143-144°	$C_{10}H_{12}ClN_5$	14.92	14.66	29.47	29.08
IX	$N(CH_2)_6$	118°	$C_{11}H_{14}ClN_5$	14.09	14.04	27.82	27.62
IX	3-methyl morpholino	210-211°	$C_{10}H_{12}ClN_5O$	13.98	13.99	27.61	27.50
IX	$N(CH_3)_2$	199°	$C_7H_8ClN_5$	17.94	17.54	35.44	35.48
IX	$N(CH_2CH_2OC_2H_5)_2$	85°	$C_{13}H_{20}ClN_5O_2$	11.30	11.37	22.32	22.30
IX	$OCH_2CH_2N(CH_3)_2$	123°	$C_9H_{12}ClN_5O$	14.67	14.68	28.98	28.96
IX	$OCH_2CH_2CH_2N(CH_3)_2$	85°	$C_{10}H_{14}ClN_5O$	13.87	13.83	27.39	27.26
IX	OCH_2CH_2NH pyridino	155°	$C_{12}H_{11}ClN_6O$	12.20	12.14	28.91	28.98
IX	OCH_3	181-183°	$C_6H_5ClN_4O$	19.20	18.86	30.35	29.96
IX	OC_6H_5	114°	$C_{11}H_7ClN_4O$	14.37	14.18	22.71	22.55
IX	OC_6H_4-*p*-$NHCOCH_3$	228°	$C_{13}H_{10}ClN_5O_2$	11.67	11.60	23.06	23.12
X	OC_6H_5 (b)	201°	$C_{11}H_8N_4O$			26.40	26.34

(a) Carbon, Calcd. (Found):59.09(59.45%), Hydrogen, Calcd. (Found): 6.45 (6.60%). (b) Carbon, Calcd. (Found): 62.25 (61.85%), Hydrogen, Calcd. (Found): 3.80 (3.51%).



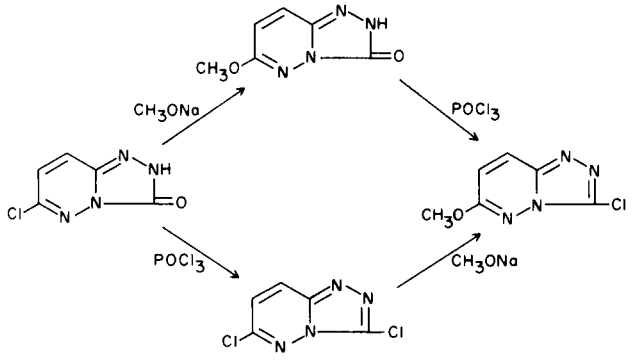
II III

The presence of an electron-attracting group at the 6-position of 3-chloropyridazine is apparently necessary for this reaction to take place since this reaction in fact did not occur in the absence of the said group. Compound III was also obtained by reacting 6-chloro-3-hydrazinopyridazine with ethyl chlorocarbonate.

Compound III was further employed for the introduction of amino groups, particularly at the 3-position, where substitution cannot be readily accomplished by means of the above methods (Chart I). Compound III reacted *via* its sodium salt with various aminoalkyl halides to give 2-aminoalkyl derivatives IV, as evidenced by the presence of a carbonyl group in their IR spectra. Compound III was also further chlorinated with phosphorus oxychloride to give 3,6-dichloro-*s*-triazolo[4,3-*b*]pyridazine (VIII). Compound VIII, when reacted at high temperature with an excess of an aliphatic amine, underwent substitution of the two chloro atoms giving the corresponding diamino compounds XI. At lower temperatures, however, only one of the two chloro atoms was substituted either by aliphatic amines or alkoxy groups (IX). To determine the exact position of substitution in the compound IX, the morpholino derivative was dehalogenated by catalytic hydrogenation. One of the two following isomers could be formed:

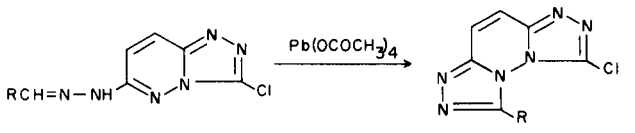
a) b)

The compound obtained (X, R = morpholino) was found to be identical to 6-morpholino-*s*-triazolo[4,3-*b*]pyridazine prepared by other methods (15), thus allowing the assignment of structure *a* for amines IX. The same structure *a* was demonstrated for the alkoxy derivatives IX, by similarly synthesizing the phenoxy derivative, which proved to be identical to the otherwise prepared (16) 6-phenoxy-*s*-triazolo[4,3-*b*]pyridazine, and by synthesizing 3-chloro-6-methoxy-*s*-triazolo[4,3-*b*]pyridazine through different methods:



Compounds of structure *b* were obtained by reversing the above reaction steps; 6-chloro-2,3-dihydro-*s*-triazolo-[4,3-*b*]pyridazine-3-one (III) was dehalogenated with Pd/C to the corresponding V which was converted with phosphorus oxychloride to VI, and finally, by condensation of the 3-chloro derivative VI with the appropriate amines, compounds VII were obtained (Chart I).

In addition, compound IX (R = $NH\text{-}NH_2$) was cyclized *via* its Schiff's base (XII) by oxidation with lead tetraacetate according to the method of Pollak and Tisler (11) to give a tricyclic system XIII. The presence of a Cl atom in compound XIII opens the way to new derivatives.



XII XIII

EXPERIMENTAL

6-Chloro-2,3-dihydro-*s*-triazolo[4,3-*b*]pyridazine-3-one (III).

Method A.

A mixture of 4.5 g. of 3,6-dichloropyridazine, 6.6 g. of semicarbazide hydrochloride and 30 ml. of 75% ethanol in presence of some drops of hydrochloric acid was heated to boiling for 18 hours. The yellow solution was filtered (charcoal) and then was cooled to 0°. The precipitate was collected by filtration to give, by crystallization from ethanol, 2.5 g. of III, m.p. 275° (yellow).

Anal. Calcd. for $C_5H_3ClN_4O$: N, 32.85; Cl, 20.79; O, 9.38. Found: N, 32.81; Cl, 20.99; O, 9.56.

Method B.

A mixture of 3.6 g. of 3-chloro-6-hydrazinopyridazine, 1.7 g. of potassium hydroxide and 3.0 g. of ethyl chlorocarbonate was refluxed in 70 ml. of 95% ethanol for 2-3 hours and then evaporated to dryness at reduced pressure. The residue was dissolved in 10 ml. of 5% aqueous potassium hydroxide, filtered and acidified with 37% hydrochloric acid. The precipitate was collected and crystallized from 99% ethanol to give 1.8 g. of III, m.p. 269-270°.

Anal. Calcd. for $C_5H_3ClN_4O$: N, 32.85; Cl, 20.79. Found: N, 32.90; Cl, 20.62.

6-Methoxy-2,3-dihydro-*s*-triazolo[4,3-*b*]pyridazine-3-one.

To a solution of sodium methoxide (from 0.27 g. of sodium) in 13 ml. of methanol and 40 ml. of anhydrous dioxane was added 1 g. of compound III. The mixture was refluxed for 40 hours and evaporated to dryness; the residue was dissolved in water, filtered and acidified with 20% hydrochloric acid to give 0.5 g. of product, m.p. 262-266° dec.

Anal. Calcd. for $C_6H_6N_4O_2$: N, 33.72. Found: N, 33.33.

6-Chloro-2,3-dihydro-2-(2-diethylaminoethyl)-*s*-triazolo[4,3-*b*]-pyridazine-3-one (IV, R = $CH_2CH_2N(C_2H_5)_2$).

To a solution of sodium methoxide in 100 ml. of methanol (from 1.4 g. of sodium) was added 9.5 g. of III and the resulting solution was evaporated at reduced pressure. The solid residue, after being washed with ether, filtered and dried, was suspended in 200 ml. of anhydrous toluene to which was added 8.3 g. of diethylaminoethyl chloride. The mixture was refluxed for 6 hours, cooled, washed with a small amount of water and dried (sodium sulfate). Evaporating at reduced pressure, followed by distillation of the oily residue gave 6.6 g. of product, b.p. 145° (3 mm); IR (sodium chloride), 1725 cm^{-1} (ν C=O).

Anal. Calcd. for $C_{11}H_{16}ClN_5O$: Cl, 13.14; N, 25.97. Found: Cl, 13.42; N, 26.18.

Similarly prepared were IV (R = $CH_2COOC_2H_5$), m.p. 110°, IR (sodium chloride), 1745-1760 cm^{-1} (ν C=O); IV (R = CH_2CH_2 morpholino), m.p. 178-179°, IR (potassium bromide), 1730 cm^{-1} (ν C=O).

2,3-Dihydro-*s*-triazolo[4,3-*b*]pyridazine-3-one (V).

A solution of 3.4 g. of III, 7.6 ml. of concentrated ammonium hydroxide in 250 ml. of methanol was hydrogenated at 2-3 atmospheres in the presence of 1.8 g. of 5% Pd/C. After adsorption was accomplished, the solution was filtered (twice) to remove the catalyst, neutralized and evaporated at reduced pressure, to give 1.3 g. of V, m.p. >260° (water).

Anal. Calcd. for $C_5H_4N_4O$: N, 41.17; O, 11.75. Found: N, 41.44; O. 12.21.

3-Chloro-*s*-triazolo[4,3-*b*]pyridazine (VI).

A mixture of 1.5 g. of V and 6 ml. of phosphorus oxychloride was refluxed 5 hours, cooled and cautiously poured into ice-water, using external cooling and stirring. The aqueous mixture was extracted with chloroform and the extract was dried (sodium sulfate) and evaporated at reduced pressure to give 0.6 g. of VI, m.p. 190° (benzene).

Anal. Calcd. for $C_5H_3ClN_4$: Cl, 22.94; N, 36.25. Found: Cl, 22.56; N, 36.90.

3-Morpholino-*s*-triazolo[4,3-*b*]pyridazine (VII).

One g. of compound VI was suspended in 10 ml. of morpholine and heated 16 hours at 120°. After cooling and evaporating the mixture *in vacuo*, the residue was triturated with 0.1 *N* sodium hydroxide and extracted with ether. The ether extract was washed with water, dried (sodium sulfate) and evaporated. Crystallization of the residue from a benzene-petroleum ether mixture gave 0.4 g. of VII (R = morpholino) m.p. 208°.

Anal. Calcd. for $C_9H_{11}N_5O$: C, 52.67; H, 5.40; N, 34.13. Found: C, 52.47; H, 5.42; N, 34.00.

Similarly prepared was compound VII, (R = piperidino) m.p. 124-125°.

3,6-Dichloro-*s*-triazolo[4,3-*b*]pyridazine (VIII).

A mixture of 5.1 g. of III and 16.5 ml. of phosphorus oxychloride was refluxed 5 hours, cooled, cautiously poured into ice

water and extracted with chloroform. After drying (calcium chloride), evaporation at reduced pressure of the solvent gave 3.2 g. of VIII, m.p. 138-139° (benzene-cyclohexane, yellow).

Anal. Calcd. for $C_5H_2Cl_2N_4$: Cl, 37.52; N, 29.64. Found: Cl, 37.11; N, 29.39.

3-Chloro-6-amino-substituted-*s*-triazolo[4,3-*b*]pyridazine (IX).

Method A.

A mixture of 1.9 g. of the chloride VIII, 1.2 g. of hydrazine hydrate and 20 ml. of 99% ethanol was refluxed 5 hours. The precipitate gave 1.5 g. of IX (R = $NHNH_2$), m.p. 208° (water).

Anal. Calcd. for $C_5H_5ClN_6$: Cl, 19.21; N, 45.53. Found: Cl, 18.73; N, 45.30.

Similarly prepared were IX (R = $NHCH_2CH_2N(C_2H_5)_2$) refluxing 8 hours, m.p. 128°; IX (R = $N(CH_2CH_2OH)_2$), refluxing 24 hours, m.p. 169°.

Method B.

A mixture of 1.9 g. of chloride VIII, 5.2 g. of morpholine and 50 ml. of toluene was stirred at room temperature 10 hours, left to stand 2 days and filtered to collect the precipitate which was triturated with acetone, filtered (charcoal), and evaporated at reduced pressure giving a residue of IX (R = morpholino), 1.6 g., m.p. 161-162° (30% ethanol).

Anal. Calcd. for $C_9H_{10}ClN_5O$: Cl, 14.79; N, 29.22. Found: Cl, 14.77; N, 29.39.

Similarly prepared were IX (R = piperidino) m.p. 143-144°; IX (R = $N(CH_2)_6$) m.p. 118° (soluble in toluene); IX (R = 3-methylmorpholino) m.p. 210-211°.

Method C.

One and six-tenths g. of chloride VIII and 8.2 ml. of 35% aqueous methylamine were dissolved in 35 ml. of boiling water and gently refluxed 2-3 hours to give a bulky precipitate which, after standing at room temperature 12 hours, was collected and purified by boiling in 99% ethanol to give 1.2 g. of IX (R = $NHCH_3$), m.p. 266°.

Anal. Calcd. for $C_6H_6ClN_5$: Cl, 19.31; N, 38.14. Found: Cl, 19.25; N, 38.22.

The yellow product, upon treatment with 37% hydrochloric acid gave the hydrochloride, m.p. 270° (white).

Similarly prepared were IX (R = $N(CH_3)_2$), refluxing 1 hour, m.p. 199°; IX (R = $N(CH_2CH_2OC_2H_5)_2$), refluxing 5 hours, m.p. 85°; IX (R = $NHNH_2$), refluxing 5 hours, m.p. 208°.

Method D.

A mixture of 1.9 g. of chloride VIII, 1.8 g. of ethyl *p*-aminophenylacetate, 1 ml. of α-picoline and 60 ml. of ethanol, was heated at 160° for 15 hours, filtered (charcoal) and concentrated to 1/3. Standing 12 hours at 0° gave 1 g. of IX (R = $NH{\cdot}C_6H_4{\cdot}CH_2COOC_2H_5$), m.p. 171° (95% ethanol, yellow).

Anal. Calcd. for $C_{15}H_{14}ClN_5O_2$: Cl, 10.69; N, 21.11. Found: Cl, 10.77; N, 21.09.

6-Acetylidenhydrazino-3-chloro-*s*-triazolo[4,3-*b*]pyridazine (IX).

The hydrazino compound IX (R = $NHNH_2$) (0.5 g.) was dissolved in 60 ml. of hot 99% ethanol and the solution was cooled to 60°. An ethanolic solution of 0.6 ml. of acetaldehyde was added and the temperature was maintained at 60° for 30 minutes. Cooling to 0° gave, after filtration on sinterized glass, 0.4 g. of XII (R = CH_3), m.p. 260° (ethanol). The IR spectrum revealed a structure: $CH_3CH{=}N{-}N{=}C$.

Anal. Calcd. for $C_7H_7ClN_6$: Cl, 16.83; N, 39.90. Found: Cl, 16.89; N, 39.79.

3-Chloro-6-alkoxy-*s*-triazolo[4,3-*b*]pyridazine (IX).

To 2-diethylaminoethanol (1.5 g.) in 40 ml. of anhydrous dioxane was cautiously added 0.8 g. of an oily suspension of sodium hydride 50%, together with 2.8 g. of chloride VIII in 10 ml. of anhydrous dioxane. The mixture was stirred at room temperature 20 hours and evaporated to dryness. Extraction of the residue with chloroform, washing with water, drying (sodium sulfate), and further evaporation gave 0.9 g. of IX (R = $OCH_2CH_2N(C_2H_5)_2$), m.p. 123° (benzene-petroleum ether).

Anal. Calcd. for $C_{11}H_{16}ClN_5O$: Cl, 13.14; N, 25.97. Found: Cl, 13.24; N, 25.96.

Similarly prepared were IX (R = $OCH_2CH_2CH_2N(CH_3)_2$), m.p. 85°; IX (R = OCH_2CH_2NH-α-pyridino), m.p. 155°; IX (R = OC_6H_4-*p*-$NHCOCH_3$), refluxing 12 hours, m.p. 228°; IX (R = OC_6H_5), refluxing 3 hours, m.p. 113-114°; IX (R = OCH_3), m.p. 182-183°, U.V. λ max (methanol) 275 mμ (ε, 3,180).

Last compound was also prepared by chlorination with phosphorus oxychloride of 6-methoxy-2,3-dihydro-*s*-triazolo[4,3-*b*]-pyridazine-3-one as for compound VIII, m.p. 181°, mixed m.p. 182-183°, U.V. λ max (methanol) 275 mμ (ε, 3,270).

Anal. Calcd. for $C_6H_5ClN_4O$: Cl, 19.20; N, 30.35. Found: Cl, 19.00; N, 30.56.

6-Substituted-*s*-triazolo[4,3-*b*]pyridazine (X).

An ethanolic suspension of 0.8 g. of 5% Pd/C was added to a solution of 1.7 g. of IX (R = morpholino), 15.4 ml. of *N*/2 sodium hydroxide and 220 ml. of 90% ethanol. The mixture was hydrogenated at 2-3 atmospheres, filtered (twice) to remove the catalyst and evaporated at reduced pressure. The dry solid residue was triturated in acetone and filtered; the filtrate was evaporated to give, after crystallization from water, the product X (R = morpholino) m.p. 182° (ethyl acetate), (lit. 184-185°) (15).

Anal. Calcd. for $C_9H_{11}N_5O$: N, 34.13; O, 7.79. Found: N, 34.12; O, 7.91.

Similarly prepared was compound X (R = phenoxy), m.p. 201° (lit. m.p. 202.5°) (16).

3,6-Diamino-substituted-*s*-triazolo[4,3-*b*]pyridazine (XI).

Method A.

A mixture of 1.9 g. of chloride VIII and 5.2 g. of morpholine was refluxed 5 hours, basified and extracted with chloroform. After drying (sodium sulfate) and evaporation of the organic layer at reduced pressure, the residue was purified by chromatography to give 1 g. of XI (R = morpholino), m.p. 223°.

Anal. Calcd. for $C_{13}H_{18}N_6O_2$: C, 53.78; H, 6.25; N, 28.95. Found: C, 54.03; H, 6.33; N, 29.03.

Method B.

A mixture of 1.9 g. of chloride VIII, 8.5 g. of piperidine and 20 ml. of 99% ethanol was maintained for 12 hours at 160°, cooled and evaporated at reduced pressure to dryness. The oily residue, when triturated with water, changed to a cream-colored solid which, after crystallization from benzene-petroleum ether, gave 1 g. of XI (R = piperidino) m.p. 116°.

Anal. Calcd. for $C_{15}H_{22}N_6$: C, 62.91; H, 7.74; N, 29.35. Found: C, 62.68; H, 7.88; N, 29.03.

3-Chloro-6-methyl-(bis-*s*-triazolo[4,3-*b*;3′,4′-*f*]pyridazine) (XIII).

A suspension of 2.2 g. of XII (R = CH_3) in 25 ml. of glacial acetic acid was added to 5.1 g. of lead tetraacetate with stirring, while the temperature rose slowly to 50°. The red solution was kept 1 hour at 50°, stirred 2 hours at room temperature, diluted with 50 ml. of water, and neutralized to *p*H 7 with sodium carbonate. After standing 1 hour, the mixture was filtered to remove

solid precipitate (XII) and the filtrate was extracted with chloroform which, after evaporation, gave a mixture which was purified by chromatography to give 1 g. of XIII (R = CH_3), m.p. 264° dec. (methanol).

Anal. Calcd. for $C_7H_5ClN_6$: C, 40.30; H, 2.42; Cl, 17.00; N, 40.29. Found: C, 40.40; H, 2.40; Cl, 16.94; N, 40.66.

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