chloride content and mixed melting point) as the hydrochloride of the starting pyrroline.

A portion (1.2 g.) of the material melting at about 150° was recrystallized from isopropyl alcohol, giving 0.86 g. of γ-benzoylamino-α,α-diphenylbutyrophenone (III, R = C_6H_5, R′ = COC_6H_5), m.p. 150.7–151.4°; near infrared absorption: secondary amide maximum absorption at 2.95 μ, ε 57 (*c* 0.21% in carbon tetrachloride).

Anal. Calcd. for $C_{29}H_{25}NO_2$ (419.50): C, 83.03; H, 6.01; N, 3.34. Found: C, 82.85; H, 6.19; N, 3.27.

1-Propionylamino-3,3-diphenylhexan-4-one (III, R = C_2H_5, R′ = COC_2H_5).—2-Ethyl-3,3-diphenyl-Δ¹-pyrroline (I, R = C_2H_5) (5 g., 20 mmoles) and 5 ml. (38 mmoles) of propionic anhydride were refluxed for three hours in a boiling water-bath; 40 ml. of water was added, and the mixture was extracted with a total of 120 ml. of diethyl ether. The organic layer was washed, dried over potassium carbonate and evaporated. The remaining oil (4.64 g.) was dissolved in 15 ml. of ethyl acetate. No crystallization occurred after 24 hours at −15°. A suitable dilution of the mixture showed an increasing ultraviolet absorption toward shorter wave lengths. The ethyl acetate was evaporated, and the remaining oil (4.61 g.) was refluxed for 30 minutes with 2.5 ml. of hydrochloric acid and 20 ml. of isopropyl alcohol. The solution was concentrated to 15 g., treated with 10 ml. of water and evaporated to 15 g. as above. The precipitate, weighing 1.30 g. (4.0 mmoles, 20.0%) melted at 125.0–127.0° and showed α,α-diphenyl ketone absorption.

A portion (1.25 g.) was recrystallized from 15 ml. of isopropyl alcohol and 15 ml. of water, yielding 0.75 g. of 1-propionylamino-3,3-diphenylhexan-4-one (III, R = C_2H_5, R′ = COC_2H_5), m.p. 134.5–135.5°; ultraviolet absorption: α,α-diphenyl ketone, principal maxima at 268.3 mμ (ε 465) and 299.7 mμ (ε 470); near infrared absorption: secondary amide maximum at 2.95 μ, ε 76 (*c* 0.13% in carbon tetrachloride).

Anal. Calcd. for $C_{21}H_{25}NO_2$ (323.42): C, 77.98; H, 7.79; N, 4.33. Found: C, 77.9; H, 7.83; N, 4.56.

N-*p*-Toluenesulfonyl-2-ethylidene-3,3-diphenylpyrrolidine (II, R = CH_3CH, R′ = $SO_2C_6H_4pCH_3$).—2-Ethyl-3,3-diphenyl-Δ¹-pyrroline (I, R = C_2H_5) (10 g., 40 mmoles) was refluxed with 8 g. (42 mmoles) of *p*-toluenesulfonyl chloride in 20 ml. of benzene for two hours. The solvent was evaporated and the residue was crystallized from 25 ml. of isopropyl alcohol at −15°; yield 4.5 g. (11.2 mmoles, 28%) of brownish powder, m.p. 139.5–142.0°. The product was recrystallized four times from isopropyl alcohol, yielding 3.10 g. of white, glistening crystals of N-*p*-toluenesulfonyl-2-ethylidene-3,3-diphenylpyrrolidine (II, R = CH_3CH, R′ = $SO_2C_6H_4CH_3$-*p*), m.p. 141.5–142.5°; near infrared absorption: no absorption maximum between 2.85 and 3.02 μ; no secondary amide (*c* 0.19% in carbon tetrachloride).

Anal. Calcd. for $C_{25}H_{24}NO_2S$ (403.53): C, 74.41; H, 6.24; N, 3.47; S, 7.95. Found: C, 74.5; H, 6.36; N, 3.37; S, 8.06.

1-*p*-Toluenesulfonamido-3,3-diphenylhexan-4-one (III, R = C_2H_5, R′ = $SO_2C_6H_4CH_3$-*p*).—N-*p*-Toluenesulfonyl-2-ethylidene-3,3-diphenylpyrrolidine (II, R = CH_3CH, R′ = $SO_2C_6H_4CH_3$-*p*)(7 g., 17.4 mmoles) was refluxed for two hours with 100 ml. of isopropyl alcohol and 10 ml. of hydrochloric acid. After standing for 30 hours at −15°, the precipitate was collected and dried; yield 2.52 g. (6.0 mmoles, 34.5%), m.p. 147.0–149.4°.

A portion (1.98 g.) was recrystallized from 45 ml. of isopropyl alcohol and dried at 60° *in vacuo*, giving 1.65 g. of 1-*p*-toluenesulfonamide-3,3-diphenylhexan-4-one (III, R = C_2H_5, R′ = $SO_2C_6H_4CH_3$-*p*), m.p. 151.2–153.0°; ultraviolet absorption: secondary sulfonamide maximum absorption at 2.99 μ, ε 66 (*c* 0.17% in carbon tetrachloride).

Anal. Calcd. for $C_{25}H_{27}NO_3S$ (421.27): C, 71.27; H, 6.46; N, 3.32; S, 7.62. Found: C, 71.6; H, 6.49; N, 3.32; S, 7.58.

Micro-analyses are by Mr. A. Sels, Analytical Department. Melting points are uncorrected and were determined on a Hershberg–Tottoli apparatus (Büchi). Titrations were performed in glacial acetic acid, using 0.02 *N* perchloric acid in the same solvent as a titrant. The titrations were followed potentiometrically (glass–calomel electrodes). All substances of structure II and III are devoid of basic properties.

Ultraviolet and near-infrared spectra were measured with a Beckman DK2-ratio recording spectrophotometer in 1-cm. silica cells; 0.01 *N* hydrochloric acid in 90% isopropyl alcohol was used as a solvent for ultraviolet spectra. Near-infrared spectra were measured in carbon tetrachloride solution. Infrared spectra were measured with a Perkin–Elmer sodium chloride "Infracord" in potassium bromide disks (300 mg.) containing about 1.0 mg. of the substance.

Sulfur was determined after burning the substance in an oxygen atmosphere as described by Schöniger,[13] and titrated with barium perchlorate and thorin as an indicator, as described by Wagner.[14]

(13) W. Schöniger, *Mikrochim. Acta*, 123 (1955).

(14) H. Wagner, *ibid.*, 19 (1957).

BEERSE, BELGIUM

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some *s*-Triazolo[b]pyridazines

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A series of *s*-triazolo[b]pyridazines has been prepared for testing of biological activity. The greater number of compounds of interest were those having a basic chain attached to position 8 of the heterocyclic ring system.

The structural features present in the *s*-triazolo[*b*]pyridazine[2] moiety I related it to the purine ring system and led to interest in the preparation of certain basic derivatives for testing as antiprotozoan and pharmacodynamic agents. At the inception of this work, relatively little attention had been given to derivatives of this heterocyclic moiety since it was first investigated[3–5]; however, since that time there has been considerably more interest.[6–10] The original designation for *s*-triazolo[b]pyridazine was 2,3-triazo-7.0-pyridazine; the ring system also has been called 2,3,7-triazaindolizine. It appears that the basically-substituted triazolo-pyrimidine types of Cook, *et al.*,[11] repre-

(1) McNeil Laboratories, Philadelphia 32, Penna.

(2) Ring Index No. 706, in A. M. Patterson and L. T. Capell, "The Ring Index," Reinhold Publishing Corp., New York, N. Y., 1940 (A.C.S. Monograph 84).

(3) C. Bülow, *Ber.*, **42**, 2208, 2555 (1909).

(4) C. Bülow, *ibid.*, **42**, 2594 (1909).

(5) C. Bülow and K. Haas, *ibid.*, **43**, 1975 (1910).

(6) N. Heimbach, U. S. Patents 2,390,707; 2,432,419.

(7) Y. Kuwabara and K. Aoki, *Konishiroku Rev.*, **6**, 1 (1955); *C. A.*, **49**, 11473 (1955).

(8) K. Murobushi, Y. Kuwabara, S. Baba and K. Aoki, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **58**, 440 (1955); *C. A.*, **49**, 14544i (1955).

(9) N. Takahayashi, *J. Pharm. Soc. Japan*, **75**, 1242 (1955); **76** 765, 1296 (1956).

(10) J. Sallé, N. Pesson and H. Kornowski, *Thérapie*, **13**, 1122 (1958).

(11) J. W. Cook, R. P. Gentles and S. H. Tucker, *Rec. trav. chim.*, **69**, 343 (1950).

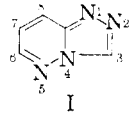
TABLE I

SUBSTITUTED 8-HYDROXY-*s*-TRIAZOLO[b]PYRIDAZINES

Substituent(s)	Yield, %[a]	Appearance[b]	Solvent[c]	M.p., °C.[d]	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
6-Methyl	74–81	Creamy prism. needles	aA	304–306 d.[e]	48.00	4.03	37.32	48.22	3.90	37.27
6,7-Dimethyl	75	Needles	aE	264–266[f]	51.21	4.91	34.13	51.20	5.09	34.29
7-Heptyl-6-methyl	33	Plates	E	170.5–171	62.88	8.12	22.56	63.01	8.31	22.62
6-(4-Chlorophenyl)	48	Cryptocrystalline	A	>320	53.56	2.86	22.72	53.81	2.68	22.67

[a] Purified products. [b] White crystalline compounds, except as noted. [c] Legend: A, acetic acid; Bu, butanol; Ch, cyclohexane; E, ethanol; Eo, ether; H, heptane; M, methanol; S, hexane; a, aqueous. [d] d. signifies melting with decomposition. [e] Previously reported[4,5] m.p. >340°. [f] Previously reported[4] m.p. 252°.

sented the closest reported approach to 8-amino-*s*-triazolo[b]pyridazines until the work of Sallé, *et al.*,[10] very recently indicated that certain 8-methylamino *s*-triazolo[b]pyridazines had cardiovascular activity.



I

Synthesis of the intermediates required for the preparation of the *s*-triazolo[b]pyridazines substituted in position 8 followed a pattern closely allied to those involved in 4-aminoquinoline types.[12] 4-Amino-1,2,4-triazole (III) interacted with a β-keto ester (II) at elevated temperatures to produce an 8-hydroxy-*s*-triazolo[b]pyridazine (IV).[4] This is close, in a formal way, to the Conrad-Limpach synthesis in the quinoline series. Earlier reports[4] to the contrary, we found no difficulty in obtaining the 8-chloro type (V) from IV (Table I) by the action of phosphorus oxychloride. The greater number of 8-(basically substituted)-*s*-triazolo[b]pyridazines (VI) were prepared by use of phenol melts, such as have been employed frequently in the 4-aminoquinolines (*e.g.*, refs. 12, 13). The products assembled in

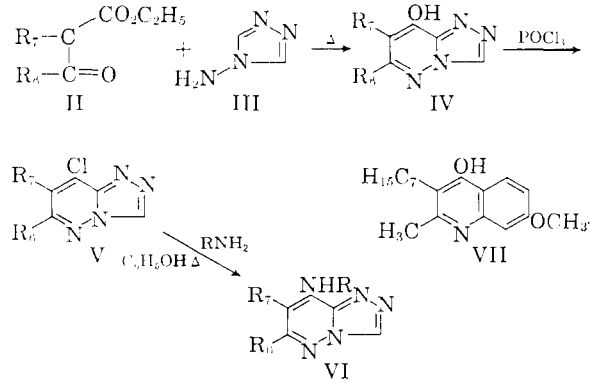


Table II were obtained from ethyl acetoacetate as the β-keto ester II; other *s*-triazolo[b]pyridazines have been presented separately (Table III). Insufficient 7-heptyl-8-hydroxy-6-methyl-*s*-triazolo[b]pyridazine was available for conversion to type VI, but it bore some resemblance to the antimalarial Endochin (VII).[14,15] The bases (VI) generally were reluctant to form readily crystallizable salts. Oxalates were most usually accessible, but were not always of precise stoichiometric composition.

(12) R. C. Elderfield, in "Heterocyclic Compounds" (R. C. Elderfield, editor), J. Wiley and Sons, Inc., New York, N. Y., 1952, Vol. 4, p. 1.

(13) E. A. Steck, L. L. Hallock and A. J. Holland, THIS JOURNAL, **68**, 129 (1946).

Experimental[16,17]

A. β-Keto Esters.—Ethyl acetoacetate was redistilled before use. Ethyl α-methylacetoacetate,[18,19] ethyl α-heptylacetoacetate[20] and ethyl 4-chlorobenzoylacetate[21] were prepared as described in the literature.

B. 8-Hydroxy-*s*-triazolo[b]pyridazines.—The reactions of 4-amino-1,2,4-triazole[22] with the several β keto-esters were carried out in much the manner described by Bülow and Haas.[5] A well-stirred mixture of the amino compound and about 1.1 equivalents of ester was placed in an oil-bath at 150°, and kept at 160–165° (external temperature) for 3 to 5 hours. To the reaction mixture there was added, during the heating, sufficient ester to total 1.25 equivalents, replacing that lost by co-distillation with the alcohol which was removed. The hot mixtures were poured out, allowed to solidify, and triturated twice with a volume of water equal to the weight of aminotriazole used, then crystallized. Compounds of this group have been listed in Table I.

C. 8-Chloro-*s*-triazolo[b]pyridazines.—Bülow and Haas[5] made note of difficulty in the conversion of 8-hydroxy-6-methyl-*s*-triazolo[b]pyridazine into the 8-chloro type. We encountered no untoward behavior when the 8-hydroxy compounds were subjected to the action of phosphorus oxychloride after the manner employed with 4-hydroxyquinolines.[13]

8-Chloro-6-methyl-*s*-triazolo[b]pyridazine[5] was obtained in 79–84% yields, long white blades from water (Darco), m.p. 190.5–191°; lit., white needles from chloroform–ligroin, m.p. 185° (red melt).

Anal. Calcd. for $C_6H_5ClN_4$: C, 42.74; H, 2.99; Cl, 21.03. Found: C, 42.43; H, 3.32; Cl, 21.20.

8-Chloro-6,7-dimethyl-*s*-triazolo[b]pyridazine was isolated in 86% yield as yellowish-white needles (m.p. 147–149°) from 90% ethanol. This product was sublimed at 130° (bath temperature) under 6×10^{-4} mm., then crystallized from ethanol; m.p. 153.5–154°.

Anal. Calcd. for $C_7H_7ClN_4$: C, 46.03; H, 3.86; N, 30.68. Found[23]: C, 45.87; H, 4.21; N, 30.82.

8-Chloro-6-(4-chlorophenyl)-*s*-triazolo[b]pyridazine, 77% yield, separated from aqueous dioxane (Darco) as brick-red needles, m.p. 240.5–241.5°.

(14) W. Salzer, H. Timmler and H. Andersag, *Chem. Ber.*, **81**, 12 (1948).

(15) W. Gingrich and E. Darrow, *Am. J. Trop. Med.*, **31**, 12 (1951).

(16) Unless otherwise noted, all melting points have been corrected for stem emergence. Boiling points are uncorrected.

(17) All analyses were performed under the direction of Mr. M. E. Auerbach and Mr. K. D. Fleischer in the Analytical Laboratories of this Institute.

(18) Prepared by the method used by Marvel and Hager[19] for ethyl *n*-butylacetoacetate.

(19) C. S. Marvel and F. D. Hager, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 248.

(20) N. J. Leonard, H. F. Herbrandson and E. M. van Heyningen, THIS JOURNAL, **68**, 1279 (1946).

(21) L. Thorp and E. R. Bushkill, *ibid.*, **37**, 1261 (1915).

(22) C. F. H. Allen and A. Bell, *Org. Syntheses*, **24**, 12 (1944).

(23) Sample somewhat hygroscopic; contained 0.58% moisture (Karl Fischer method); analyses given on dry basis.

TABLE II

8-SUBSTITUTED 6-METHYL-*s*-TRIAZOLO[b]PYRIDAZINES

8-Substituent	Base[a] or salt	Yield, %[b]	Appearance[c]	Solvent[d]	M.p., °C.[e]	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$-NHCH_2CH_2N(C_2H_5)_2$	B	88	Leaflets	H	151.5–152.5	58.04	8.12	33.85	58.15	7.94	34.15
	O	71	Microcrystals	E	173–174 d.	49.69	6.56	24.84	49.73	6.57	25.08
$-NH(CH_2)_3N(C_2H_5)_2$	B	74	Platelets	S	94.5–96	59.51	8.45	32.04	59.54	8.36	32.31
	O	73	Blades	aE	210–211	51.12	6.86	23.85	51.40	6.88	24.10
	Mi	76.5	Needles	M-Eo	205.5–207	31.39[f]		20.79	31.28[f]		20.99
$-NHCH_2CH(OH)CH_2N(C_2H_5)_2$	B	81	Platelets	H	126–127	56.09	7.97	30.19	55.90	7.67	30.20
	O	68	Microcrystals	E	167.5–169	48.90	6.57	22.82	49.13	6.75	23.21
$-NH(CH_2)_4N(C_2H_5)_2$	B	77	Microcrystals	S	81–81.5	60.84	8.75	30.41	60.52	9.01	30.19
	nO	64	Flakes	aE	145–146.5	[g]			[g]		
$-NH(CH_2)_4N(C_4H_9)_2$	B	59	Platelets	S	76–77	65.02	9.70	25.28	64.98	9.82	25.12
	nO	67	Microcrystals	aE	158–159.5	[h]			[h]		
$-NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	B	71	[i]		[i]			9.65[j]			9.60[j]
	O	74.5	Spherules	E	217–218[k]	53.66	7.42	22.09	53.75	7.21	21.92
$-NHCH_2CH(C_6H_4Cl)(CH_2)_2N(C_2H_5)_2$[m]	B	56.5	Yellowish microcryst.	H	137–138	62.08	7.04	21.72	61.90	7.60	21.78
	O	69	Fine needles	E	199.5–201	55.40	6.13	5.87[j,l]	55.62	7.62	5.80[j,l]

[a] B, base; Mi, methiodide; O, monoxalate; nO, oxalate having complex nature. [b–e] See notes *a–d* in Table I. [f] Ionic halogen. [g] Found: base, 65.50; acid, 31.30; H_2O, 1.68. [h] Found: base, 71.60; acid, 27.00; H_2O, 0.47. [i] Golden oil; b.p. *ca.* 200° (0.06 mm.). [j] Basic nitrogen; determined by perchloric acid method. [k] Sinters at 211°. [l] *Anal.* Calcd. for $C_{20}H_{27}ClN_6 \cdot H_2C_2O_4$: Cl, 7.43; base, 81.2; acid, 18.8. Found: Cl, 6.92; base, 80.9; acid, 18.9; Dumas values not concordant. [m] C_6H_4Cl = *p*-chlorophenyl.

TABLE III

8-AMINO-*s*-TRIAZOLO[b]PYRIDAZINE TYPES

Substituents	Base[a] or salt	Yield, %[b]	Appearance[c]	Solvent[d]	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
8-(2-Diethylaminoethylamino)-6,7-dimethyl-	B	67.5	Creamy blades	Ch	96.5–98	59.51	8.45	10.68[e]	59.57	8.71	10.60[e]
	nO	79	Needles	aE	213–215	[f]			[f]		
8-(4-Diethylamino-1-methylbutylamino)-6,7-dimethyl-	B	50.5	Blades	Ch	97–98.5	63.12	9.27	9.20[e]	63.60	9.35	9.51[e]
	Mi	63	Rhombs	M-Eo	196.5–198	28.43[g]		18.83	28.30[g]		18.76
6-(4-Chlorophenyl)-8-(3-diethylamino-2-hydroxypropylamino)-	B	41	Prismatic ndls.	Bu	191.5–192.5	57.67	6.18	22.43	57.65	5.89	22.60
6-(4-Chlorophenyl)-8-(4-diethylamino-1-methylbutylamino)-	B	39	Microcrystals	Eo	125.5–126.5	62.08	7.04	21.72	61.89	6.99	21.70

[a–d] As given in Table II (q.v.). [e] Basic nitrogen. [f] Found: base, 73.8; acid, 26.0. [g] Ionic halogen.

Anal. Calcd. for $C_{11}H_{16}Cl_2N_4$: C, 49.83; H, 2.28; N, 21.14. Found: C, 49.63; H, 2.27; N, 20.99.

D. 8-Amino-*s*-triazolo[b]pyridazine Types.—The general pattern employed in the conversion of the 8-chloro-*s*-triazolo[b]pyridazines to the compounds bearing a basic chain was that which we applied to 4-chloroquinolines.[13] 4-Dibutylaminobutylamine[24] and 2-(4-chlorophenyl)-4-diethylaminobutylamine[25,26] were prepared for this work; the other amines were readily available. The greater number of the products were distilled at 10^{-4} mm. prior to crystallization; some of the liquid bases were purified by distribution between phosphate buffers and methylene chloride and redistilled to obtain satisfactory material. All 6-methyl-*s*-triazolo[b]pyridazines bearing a basic chain in position 8 have been placed in Table II; the related 6,7-dimethyl- and 6-(4-chlorophenyl)-*s*-triazolo[b]pyridazines have been presented separately (Table III).

8-Amino-6-methyl-*s*-triazolo[b]pyridazine was made after the method of Jacini.[27] A mixture comprised of 50.7 g. (0.3 mole) of 8-chloro-6-methyl-*s*-triazolo[b]pyridazine and 59.1 g. (1 mole) of acetamide in 150 g. of phenol was stirred well and heated at 165–170° while a stream of ammonia gas was bubbled through it for 6 hours. The cooled magma was diluted with an equal volume of benzene, and a solid collected. After acidifying the filtrates with hydrochloric acid, the solid and the filtrates were each extracted with 4 *N* hydrochloric acid, then the acidic extracts were basified with 50% sodium hydroxide and chilled. A maroon solid was isolated which gave 23.1 g. (52% yield) of garnet blades after one crystallization from aqueous methanol (Darco) and three from water; m.p. 222–223°.

Anal. Calcd. for $C_6H_7N_5$: C, 48.31; H, 4.73; N, 46.96. Found: C, 38.40; H, 4.78; N, 46.69.

E. Salts of 8-Amino-*s*-triazolo[b]pyridazine Types. Oxalates.—The oxalates were prepared by the addition of an ethyl acetate solution of two equivalents of anhydrous oxalic acid to an ethyl acetate solution of the appropriate base. In some cases, when gummy material was deposited on the walls of the flask, it was expedient to remove the slurry of solid for work and reject the gum. A few of the oxalates were best purified by dissolving the crude meterial in water and then adding ethanol. All oxalates (Tables II and III) were dried at 100° (0.5 mm.); most gave analytical values corresponding to mono-oxalates.

Some oxalates presented particular difficulties on elementary analysis.[17] In these cases, the assay on base content was accomplished by the perchloric acid method for basic nitrogen,[28] and the oxalic acid determined volumetrically with standard potassium permanganate after decomposition of calcium oxalate obtained from the salt of the organic base.

Methiodides.—All methiodides were prepared in methanol using four equivalents of methyl iodide. The mixtures were refluxed briefly (to half an hour) before precipitation with absolute ether. Only monomethiodides resulted (Tables II and III).

Acknowledgment.—We wish to express appreciation to Dr. C. M. Suter for his continued friendly interest in and encouragement of our work with heterocyclic types.

RENSSELAER, N. Y.

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(27) G. Jacini, *Gazz. chim. ital.*, **70**, 624 (1940).

(28) G. Toennies and T. P. Callan, *J. Biol. Chem.*, **125**, 259 (1938).