period of 2 to 3 hours in an atmosphere of nitrogen. If during the addition of the halide solution to the couple the reaction became too vigorous a water-bath was used to cool the contents of the flask momentarily. The mixture was then allowed to stand overnight. The flask was connected to a simple vacuum distillation system and any unreacted halides were removed at 100 mm. pressure. The pressure was then reduced to approximately 15 mm. and the dialkyl zinc compound which distilled was collected in a graduated receiver. All connections of the apparatus were of good quality cork generously coated with a very heavy stopcock grease. In the case of dimethylzinc, distillation was effected at atmospheric pressure in a current of nitrogen. The yield of the dialkyl zinc compound was based on this once distilled material.

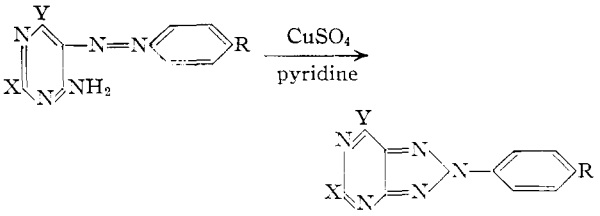
DEPARTMENT OF CHEMISTRY
VIRGINIA POLYTECHNIC INSTITUTE
BLACKSBURG, VIRGINIA

v-Triazolo(d)pyrimidines. II. Further Studies in the 2-Aryl Series

BY L. W. HARTZEL AND F. R. BENSON

RECEIVED DECEMBER 23, 1953

Additional 2-aryl-v-triazolo(d)pyrimidines have been prepared in this Laboratory since those reported previously.[1] These include further examples of 5-amino-7-hydroxy- as well as 5,7-diamino- and 7-amino-5-methylmercapto derivatives. These compounds were prepared by the oxidation of the corresponding 4-amino-5-arylazopyrimidines in the manner originally described.



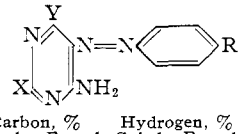
where X = NH_2 or CH_3S and Y = NH_2 or OH

One of the compounds reported in this note, 2-phenyl-5,7-diamino-v-triazolo(d)pyrimidine, has been described elsewhere[2] along with other members of this class.

In Table I there are listed the formulas and analyses of the 4-amino-5-arylazopyrimidines prepared. Some of these compounds contain water of crystallization which it was found impractical to remove. Calculated carbon to nitrogen ratios for these compounds agreed well with the theo-

TABLE I

4-AMINO-5-ARYLAZOPYRIMIDINES[a]

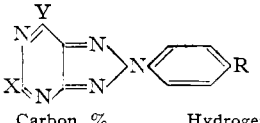


X	Y	R	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon/Nitrogen Calcd.	Carbon/Nitrogen Found
NH_2	OH	*p*-$COOC_4H_9$	$C_{15}H_{18}N_6O_3 \cdot 1^1/_2H_2O$	50.41	50.5	5.92	5.4	23.52	23.8	2.143	2.122
NH_2	OH	*p*-$CONH_2$	$C_{11}H_{11}N_7O_2$	48.35	47.9	4.06	4.2	35.89	35.7	1.347	1.342
NH_2	OH	*p*-OH	$C_{10}H_{10}N_6O_2 \cdot 2H_2O$[b]	42.55	42.4	5.00	4.54	29.78	29.8	1.429	1.423
NH_2	OH	*p*-SO_3H	$C_{10}H_{10}N_6O_4S \cdot H_2O$	36.58	36.3	3.69	3.8	25.60	25.5	1.429	1.424
NH_2	NH_2	H	$C_{10}H_{11}N_7$[c]	52.39	52.9	4.83	4.8	42.77	43.0	1.225	1.230
NH_2	NH_2	*p*-COOH	$C_{11}H_{11}N_7O_2 \cdot H_2O$	45.35	45.5	4.50	4.3	33.67	33.4	1.347	1.362
NH_2	NH_2	*p*-CONHCHCOOH $(CH_2)_2COOH$	$C_{16}H_{18}N_8O_5 \cdot H_2O$[d]	45.71	45.7	4.80	4.7	26.66	26.3	1.715	1.738
CH_3S	OH	H	$C_{11}H_{11}N_5OS$[e]	50.56	50.8	4.24	4.2	12.27[f]	12.2[f]		
CH_3S	OH	*p*-COOH	$C_{12}H_{11}N_5O_3S$	47.20	47.1	3.63	3.8	10.50[f]	10.6[f]		

[a] All the compounds decompose above 300° unless otherwise specified. [b] Decomposes 243°. [c] Begins to decompose at 235°. [d] Decomposes 270°. *p*-Aminobenzoyl-l(+)glutamic acid was used as starting material. [e] Decomposes 260°. [f] Sulfur values.

TABLE II

2-ARYL-V-TRIAZOLO(d)PYRIMIDINES[a]



X	Y	R	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
NH_2	OH	*p*-$COOC_4H_9$	$C_{15}H_{16}N_6O_3$	54.87	55.2	4.91	4.4	25.60	25.8
NH_2	OH	*p*-$CONH_2$	$C_{11}H_9N_7O_2$	48.71	48.3	3.34	3.4	36.15	36.1
NH_2	OH	*p*-OH	$C_{10}H_8N_6O_2$	49.18	49.2	3.30	3.3	34.42	33.9
NH_2	OH	*p*-SO_3H	$C_{10}H_8N_6O_4S$	38.96	38.8	2.61	2.6	27.27	26.9
NH_2	NH_2	H[b]	$C_{10}H_9N_7$	52.85	52.8	3.99	4.2	43.15	43.2
NH_2	NH_2	*p*-COOH	$C_{11}H_9N_7O_2$	48.71	48.3	3.34	3.5	36.15	36.3
NH_2	NH_2	*p*-CONHCHCOOH[c] $(CH_2)_2COOH$	$C_{16}H_{16}N_8O_5$	48.00	47.6	4.03	4.5	27.99	27.9
CH_3S	OH	H	$C_{11}H_9N_5OS$	50.95	51.2	3.50	3.8	27.01	27.0
CH_3S	OH	*p*-COOH	$C_{12}H_9N_5O_3S$	47.52	47.3	2.99	3.1	...	..

[a] All the compounds decompose over 300° unless otherwise specified. [b] Previously described in reference 2. [c] Begins to decompose at 235°.

(1) F. R. Benson, L. W. Hartzel and W. L. Savell, THIS JOURNAL, 72, 1816 (1950).

(2) R. P. Parker and J. S. Webb, U. S. Patent 2,543,333, Feb. 27, 1951.

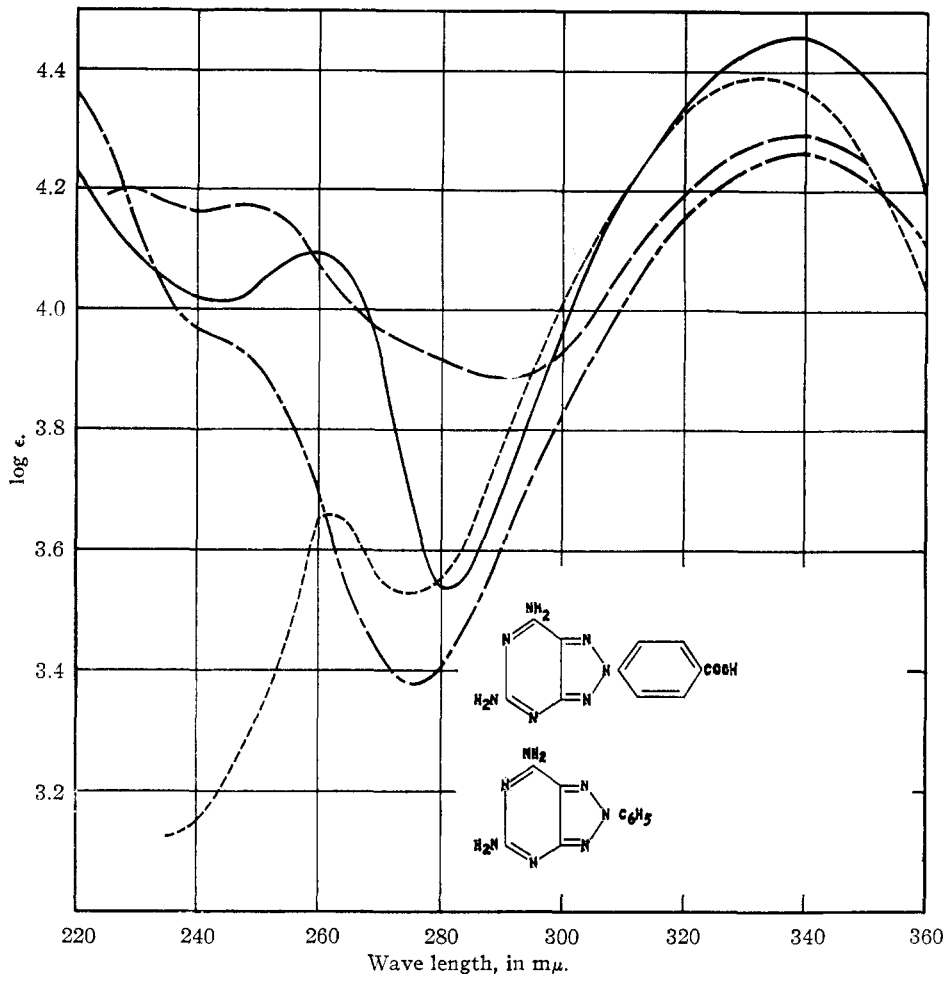


Fig. 1.—Absorption spectra of 5,7-diamino-2-phenyl-v-triazolo(d)pyrimidine (— — —, in 3 *N* NaOH; - - - - - -, in 85% H_3PO_4; ——— in concd. H_2SO_4) and 2-*p*-carboxyphenyl-5,7-diamino-v-triazolo(d)pyrimidine (— — —, in concd. H_2SO_4).

retical values. The arylazopyrimidines are high melting orange solids which are extremely insoluble in water and most of the usual solvents.

Table II lists the formulas and analyses of the new 2-aryl-v-triazolo(d)pyrimidines. These materials are high melting compounds, insoluble in water and most organic solvents, which range in color from white to pale yellow.

The ultraviolet spectrum of 5,7-diamino-2-phenyl-v-triazolo(d)pyrimidine has been determined in concentrated sulfuric acid and is depicted in Fig. 1. This compound exhibits a maximum at 340 mμ and a minimum at 275 mμ.

Ultraviolet spectra of 2-*p*-carboxyphenyl-5,7-diamino-v-triazolo(d)pyrimidine in 2 *N* sodium hydroxide, concentrated sulfuric acid, and 85% phosphoric acid have been determined and are shown in Fig. 1. The spectrum in 2 *N* sodium hydroxide solution exhibits maxima at 230, 248 and 340 mμ; these results are similar to those reported for the corresponding 7-hydroxy compound, whose spectrum was determined in 0.1 *N* sodium hydroxide solution.[1] The two spectra in acid solution exhibit maxima at 260 to 265 mμ and 330 to 340 mμ; the effect of the acid solvent is to combine the lower maxima with a shift to higher wave lengths.

Bacteriological tests of the azopyrimidines and 2-aryl-v-triazolo(d)pyrimidines, presently and previously[1] reported, indicate that the growth of *Streptococcus salivarius* and *Serratia marcescens* is slightly inhibited, while *Micrococcus pyogenes aureus*, *E. coli* and *Klebsiella pneumoniae* are not significantly affected.

In tests carried out at Sloan-Kettering Institute none of the compounds effected significant inhibition of the growth of Sarcoma 180 in mice.

Experimental

The requisite intermediate azopyrimidines were prepared by standard procedures as described in reference 1. Typical procedures used to obtain the new 2-aryl-v-triazolo(d)-pyrimidines are given below.

5-Amino-7-hydroxy-2-*p*-hydroxyphenyl-v-triazolo(d)pyrimidine.—To a hot mixture of 26.49 g. of copper sulfate pentahydrate, 54 ml. of pyridine and 54 ml. of water were added 9.89 g. (0.035 mole) of 2,4-diamino-6-hydroxy-5-*p*-hydroxyphenylazopyrimidine dihydrate and 34 ml. of pyridine. After refluxing with stirring for 3 hours the mixture was poured into 600 ml. of water and the solid which precipitated filtered off and washed with water. The solid was dissolved in a minimum volume of 2 *N* sodium hydroxide solution, treated with charcoal, filtered, and precipitated by the addition of acetic acid. The precipitate was separated by centrifuging and again dissolved and precipitated as before. The crude product was finally washed with water and recrystallized from ethylene glycol. The pure product was washed first with water, then alcohol, and

ether. After drying overnight at 60° under vacuum the yield was 2.4 g. (28% of the theoretical amount).

7-Hydroxy-5-methylmercapto-2-phenyl-v-triazolo(d)pyrimidine.—A weight of 7 g. (0.027 mole) of 4-amino-6-hydroxy-2-methylmercapto-5-phenylazopyrimidine together with 25 ml. of pyridine was added to a hot mixture of 20 g. of copper sulfate pentahydrate, 40 ml. of pyridine and 40 ml. of water. The mixture was refluxed 3 hours with stirring, then poured into 400 ml. of water and acidified with hydrochloric acid. The precipitate which separated was filtered, dissolved in 1% sodium hydroxide solution, and reprecipitated with hydrochloric acid. The solid was separated by centrifuging, then dissolved in dilute ammonium hydroxide solution, treated with charcoal, and filtered. The crude product was precipitated by the addition of acetic acid and separated from the supernatant liquid by centrifuging. After recrystallization from hot dioxane the white solid was washed with ether and dried overnight at 60° under vacuum. The yield was 1.6 g. (23%).

2-*p*-Carboxyphenyl-5,7-diamino-v-triazolo(d)pyrimidine.—To a mixture of 13.3 g. of copper sulfate pentahydrate, 27 ml. of water and 27 ml. of pyridine were added 5.5 g. (0.018 mole) of 2,4,6-triamino-5-*p*-carboxyphenylazopyrimidine monohydrate and 17 ml. of pyridine. The mixture, which did not give a homogeneous solution, was refluxed with stirring for 2.5 hours, then cooled, diluted with 300 ml. of water, the precipitate filtered and washed with water. The precipitate was returned to the original reaction vessel and treated with copper sulfate and aqueous pyridine as before. The mixture was cooled, poured into water, and the precipitate filtered and washed with water until free of blue coloration. The precipitate was slurried with two portions of hot 10% acetic acid, filtered and washed with water, alcohol, and ether. The light yellow product which was dried under vacuum at 60° overnight weighed 4.7 g. (95%).

LABORATORY OF ADVANCED RESEARCH
REMINGTON RAND, INC.
SOUTH NORWALK, CONNECTICUT

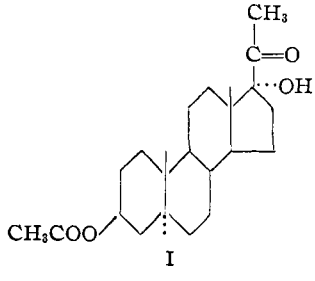
Perbenzoic Acid Oxidation of Reichstein's "L" Acetate[1]

BY NORMA S. LEEDS, DAVID K. FUKUSHIMA AND T. F. GALLAGHER

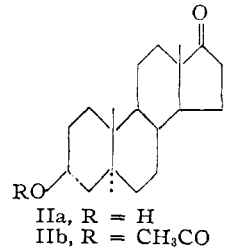
RECEIVED JANUARY 8, 1954

The oxidation of 20-ketosteroids to 17-acetoxy derivatives of steroids by perbenzoic acid is a generally known reaction.[2-4]

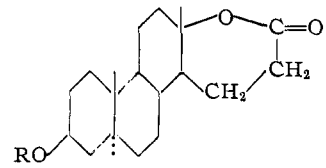
In accordance with the mechanism proposed for this reaction,[5,6] the oxidation of 3β-acetoxy-17α-hydroxyallopregnane-20-one (Reichstein's Substance "L" acetate (I)) with perbenzoic acid should yield isoandrosterone acetate (IIb).



I



IIa, R = H
IIb, R = CH_3CO



IIIa, R = H
IIIb, R = CH_3CO

When this reaction was carried out in the usual way in the presence of *p*-toluenesulfonic acid for 7 days at room temperature, the principal product obtained was isoandrololactone acetate (IIIb), a substance previously prepared by the action of peracetic acid on isoandrosterone.[7] The expected isoandrosterone acetate was obtained in only small yield. However, in the absence of the acid catalyst and with the time of reaction lessened to two days, isoandrosterone acetate was the principal product; isoandrololactone acetate was obtained only in small amounts. It appears, therefore, that the 17-ketosteroid is an intermediate in the peracid oxidation of a 17α-hydroxy-20-ketosteroid and that further reaction with the oxidant leads to the lactone III by the rupture of the C_{13}–C_{17} bond.[8]

Experimental[9]

Isoandrololactone Acetate (IIIb).—To 5 ml. of a benzene solution containing 275 mg. of 3β-acetoxy-17α-hydroxyallopregnane-20-one (I) was added 2.2 ml. of 0.65 *M* perbenzoic acid and 19 mg. of *p*-toluenesulfonic acid monohydrate in 0.025 ml. of acetic anhydride and 0.3 ml. of acetic acid. The solution was allowed to stand in the dark for 7 days at room temperature and was then diluted with ether, washed with sodium carbonate solution and with water. The solution was dried over sodium sulfate and the solvent removed under reduced pressure. The 223 mg. of product so obtained was chromatographed on 45 g. of silica gel and eluted with increasing concentration of ether–petroleum ether. Crystalline eluates were obtained with anhydrous ether and together weighed 114 mg. (43%) with melting points ranging from 145 to 155°. Recrystallization from ether–petroleum ether afforded pure isoandrololactone acetate (IIIb), m.p. 159–160°, $[\alpha]^{23}D$ −42° (dioxane), reported[7] m.p. 158.5–159.9°. The m.p. of a mixture with an authentic sample of isoandrololactone acetate[10] showed no depression. The infrared spectrum of the reaction product and the authentic sample was identical.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.41; H, 9.19. Found: C, 72.50; H, 8.83.

The early fractions of the chromatogram eluted with 40 to 50% ether–petroleum ether were combined and 36 mg. of isoandrosterone acetate identified by infrared spectrum was obtained.

Isoandrosterone (IIa).—A solution of 305 mg. of 3β-acetoxy-17α-hydroxyallopregnane-20-one (I) in 2.8 ml. of 0.35 *M* perbenzoic acid in benzene was stored for 2 days. After dilution with ether, the solution was washed with sodium carbonate and with water. The ether solution was dried over sodium sulfate and the solvent was removed under diminished pressure, leaving a residue of 213 mg. The reaction product was saponified with 3.2 ml. of 1.25 *N* sodium hydroxide in 8 ml. of methanol at room temperature overnight. Ether was added to the saponification mixture which was then washed free of base and dried over sodium sulfate. Upon evaporation of the solvent, 145 mg. of product was obtained and was chromatographed on 25 g. of silica gel. From the earlier eluates of the chromatogram, 102 mg.

(1) This investigation was supported by grants from the Anna Fuller Fund, the Lillia Babbitt Hyde Foundation, the Teagle Foundation, and the National Cancer Institute, United States Public Health Service (C-440).

(2) V. Burckhardt and T. Reichstein, *Helv. Chim. Acta*, **25**, 1434 (1942).

(3) L. H. Sarett, THIS JOURNAL, **69**, 2899 (1947).

(4) T. F. Gallagher and T. H. Kritchevsky, *ibid.*, **72**, 882 (1950).

(5) R. B. Turner, *ibid.*, **72**, 878 (1950).

(6) W. von E. Doering and L. Speers, *ibid.*, **72**, 5515 (1950).

(7) H. Levy and R. P. Jacobsen, *J. Biol. Chem.*, **171**, 71 (1947).

(8) The structure of isoandrololactone acetate (IIIb) has been inferred from the results of studies by D. Prins (unpublished findings) and C. von Seemann and G. A. Grant (THIS JOURNAL, **72**, 4073 (1950)). The tertiary oxygen adjacent to the bridgehead is consistent with their findings (see also G. M. Picha, *ibid.*, **74**, 703 (1952)).

(9) All m.p.'s are corrected.

(10) We wish to thank Dr. D. Prins for supplying a sample of isoandrololactone acetate for comparison studies.