Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.6. Found: C, 70.5; H, 5.3.

The *hydrazide* crystallized from ethanol in colorless needles, m.p. 187–188°.

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.1; H, 5.5; N, 10.9. Found: C, 65.0; H, 5.4; N, 10.8.

4'-Hydroxy-4-phenoxybenzylamine (VII). Curtius degradation of 25.8 g. of the foregoing hydrazide, effected as for the higher homolog, yielded 10 g. of the hydrochloride of VII; the free *base* obtained on alkalinization with aqueous ammonia crystallized from ethanol–petroleum ether (b.p. 35–40°) in colorless prisms, m.p. 119°.

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.5; H, 6.1; N, 6.5. Found: C, 72.6; H, 6.0; N, 6.4.

2-(4'-Methoxy-4-phenoxyphenyl)cinchoninic acid (VIII). A solution of 24 g. of 4'-methoxy-4-phenoxyacetophenone, 14.7 g. of isatin, and 16.8 g. of potassium hydroxide (dissolved in a few milliliters of water) in 85 ml. of ethanol was refluxed on the water bath for 24 hr. After addition of water, the neutral impurities were extracted in ether and the aqueous layer was acidified with acetic acid. The solid precipitate was collected and recrystallized from acetic acid, to yield 26 g. of fine yellowish prisms, m.p. 223°.

Anal. Calcd. for $C_{23}H_{17}NO_4$: C, 74.4; H, 4.6; N, 3.8. Found: C, 74.3; H, 4.8; N, 3.6.

Thermal decomposition of this acid gave a residue which was purified by vacuum distillation, furnishing after recrystallization from ethanol *2-(4'-methoxy-4-phenoxyphenyl)-quinoline* (XI), as colorless needles, m.p. 165°.

Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.7; H, 5.2; N, 4.3. Found: C, 80.7; H, 5.2; N, 4.3.

This quinoline gave a *picrate*, crystallizing from benzene in shiny yellow prisms, m.p. 190°.

2-(4'-Methoxy-4-phenoxyphenyl)-3-methylcinchoninic acid (IX). Similarly prepared from 25.7 g. of ketone I, this *cinchoninic acid* (26.2 g.) crystallized from acetic acid in pale yellow needles, m.p. 276°.

Anal. Calcd. for $C_{24}H_{19}NO_4$: C, 74.8; H, 5.0; N, 3.6. Found: C, 74.6; H, 5.0; N, 3.5.

2-(4'-Methoxy-4-phenoxyphenyl)-3-methylquinoline (XII) crystallized from ethanol in colorless needles, m.p. 118°.

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.9; H, 5.6; N, 4.1. Found: C, 80.9; H, 5.5; N, 4.0.

The *picrate* crystallized from benzene in yellow prisms, m.p. 198°.

4'-Methoxy-4-phenoxybutyrophenone. Prepared as for the lower homolog, by Friedel-Crafts reaction with 20 g. of 4-phenoxyanisole and 10.7 g. of butyryl chloride, this *ketone* (21.6 g.), b.p. 230–232°/14 mm., crystallized from ethanol in shiny colorless leaflets, m.p. 77°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.5; H, 6.7. Found: C, 75.5; H, 6.8.

A Pfitzinger reaction with 27 g. of this ketone yielded 25.9 g. of *2-(4'-methoxy-4-phenoxyphenyl)-3-ethylcinchoninic acid* (X), crystallizing from acetic acid in yellowish prisms, m.p. 295°.

Anal. Calcd. for $C_{25}H_{21}NO_4$: C, 75.2; H, 5.3; N, 3.5. Found: C, 75.2; H, 5.3; N, 3.5.

2-(4'-Methoxy-4-phenoxyphenyl)-3-ethylquinoline (XIII) crystallized from ethanol in shiny colorless prisms, m.p. 107°.

Anal. Calcd. for $C_{24}H_{21}NO_2$: C, 81.1; H, 6.0; N, 3.9. Found: C, 81.2; H, 5.9; N, 4.0.

The corresponding *picrate* crystallized from benzene in yellow needles, m.p. 189°.

4'-Methoxy-4-phenoxyisovalerophenone. This *ketone* (20 g.), b.p. 265–270°/36 mm., was prepared by a Friedel-Crafts reaction with 20 g. of 4-phenoxyanisole and 12 g. of isovaleryl chloride; it crystallized from methanol as lustrous colorless leaflets, m.p. 62°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.0; H, 7.1. Found: C, 76.1; H, 7.1.

This substance gave no cinchoninic acid under the usual conditions of the Pfitzinger reaction.

PARIS(V^e), FRANCE

[COMMUNICATION NO. 2144 FROM THE KODAK RESEARCH LABORATORIES]

The Structure of Certain Polyazaindenes. IX. Sensitivity of the Ultraviolet Absorption Spectra to *p*H Variation, and Amine Salts of Tetrazaindenes

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Ultraviolet absorbance data showing sensitivity to *p*H are reported for several polyazaindenes. The compound previously regarded as *N,N'*-bis(1,2,4-triazol-3-yl)-3-iminobutyramide is shown to be the salt of 3-amino-1,2,4-triazole and 6-methyl-4-oxo-1,3,3a,7-tetrazaindene. Other amine salts of tetrazaindenes are described.

Ultraviolet absorbance spectra recorded for aqueous solutions at acid and alkaline *p*H's demonstrate the existence of two possible structures for various tetra- and pentazaindenes and triazoles. Their extinction maxima are listed in Table I. Systematic variations in the spectra of three tetrazaindenes (I, VI, VII) observed over a range of *p*H's between 6 and 8 can be explained as representing intermediate mixtures of the neutral molecule and the anion produced by its dissociation at elevated *p*H's. Among the compounds studied, ionization appears to be negligible at *p*H 1 but complete at *p*H 10.

The present findings do not show the existence of a third, cationic structure in water, although it has been noted that 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (I) can be titrated with perchloric acid in glacial acetic acid.[1] The quaternization of these compounds with methyl *p*-toluenesulfonate is, of course, a consequence of the ionic character. Existence of an anionic structure is in agreement with previous observations that I shows one acidic hydrogen in nonaqueous (dimethylformamide)

(1) D. D. Fix, these Laboratories, private communication.

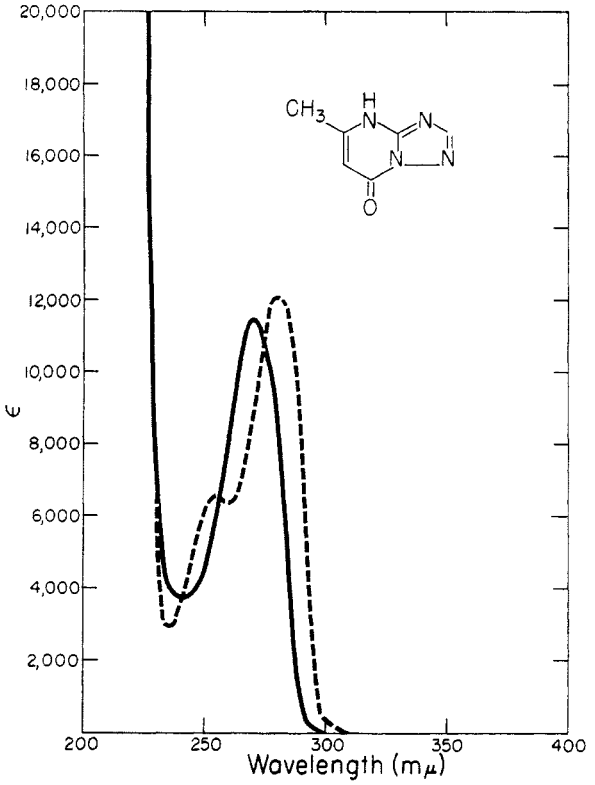


Fig. 1. Ultraviolet spectra of 6-methyl-4-oxo-1,3,3a-7-tetrazaindene: ——— at *p*H 1; - - - - - - at *p*H 10

titration with potassium methoxide,[2] and that it can be precipitated as the silver salt from neutral solution.

Under certain conditions, aminotriazole reacts with diketene or acetoacetic ester to yield I.[3,4] A by-product, once tentatively identified[5] as *N,N'*-bis(1,2,4-triazol-3-yl)-*β*-iminobutyramide (II), is now recognized to be the aminotriazole salt (III) of I. As proofs of the salt structure, the following new evidence is cited: (1) The material decomposed on attempted sublimation, yielding I as a major fraction of the sublimate. (2) It changed during repeated recrystallization from water, again with I as a chief dissociation product. (3) Based on a molecular weight equal to the sum of one mole of aminotriazole and one mole of I, its ultraviolet extinction patterns recorded at *p*H 1 and *p*H 10 were nearly identical with those of I (Fig. 1). (4) It had a distinctive infrared absorption spectrum differing from that[6] of I but identical with that of a compound prepared from a 1:1 molecular mixture of I and the aminotriazole (Fig. 2). It

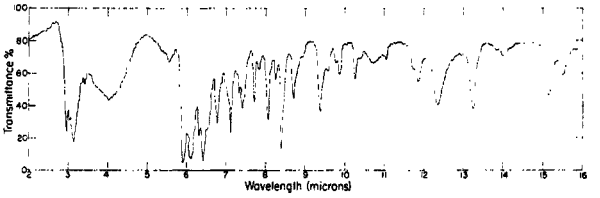


Fig. 2. Infrared spectrum of known 3-amino-1,2,4-triazole salt of 6-methyl-4-oxo-1,3,3a-7-tetrazaindene

The infrared measurements were made in a Baird double-beam recording spectrophotometer using sodium chloride optics; the samples were prepared as pressed plates in potassium bromide

should be pointed out that the conditions of crystallization are critical in preparation of the salt; this is probably a reason for its late recognition.[7] In the authors' opinion, the true nature of III is best represented by the following formula, which recognizes the salt structure while allowing for resonance contributors.

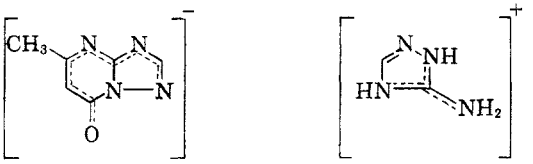


Table II includes ultraviolet extinction data for compounds of related interest. The hydrazine salt of I and the 3-amino-5-methyl-1,2,4-triazole salt of a homolog of I both show a marked similarity to I, in agreement with the postulated salt structure. A number of salts of I and various primary and secondary amines have been prepared; their ultraviolet extinction patterns also resemble those of I. Apparently I does not form salts with tertiary amines. Carbethoxy-4-oxo-tetrazines, however, not only form salts with tertiary amines (pyridine, triethanolamine, and triethylamine), but they also tend to form salts with aminotriazole more readily than I; *e.g.*, the reactions of 3-amino-1,2,4-triazole with ethyl *α*-ethoxyethylidenemalonate in acetic acid and with ethyl oxalylpropionate in ethanol yielded the aminotriazole salt of 5-carbethoxy-6-methyl-4-oxo-1,3,3a,7-tetrazaindene and 6-carbethoxy-5-methyl-4-oxo-1,3,3a,7-tetrazaindene, respectively.

EXPERIMENTAL

Reaction of 3-amino-1,2,4-triazole with ethyl α-ethoxyethylidenemalonate. A mixture of 28 g. (0.12 mole) of ethyl *α*-ethoxyethylidenemalonate and 10 g. (0.12 mole) of 3-

(2) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. Van Allan, *J. Org. Chem.*, **24**, 779 (1959); esp. 783–784.

(3) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. Van Allan, *J. Org. Chem.*, **24**, 787 (1959).

(4) N. Heimbach and W. Kelly, Jr., U. S. Patents **2,444,608** and **2,475,136**.

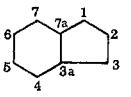
(5) Ref. 3, 788–789.

(6) Ref. 2, 785.

(7) While this paper was in preparation, the authors learned of independent work by K. Sirakawa, Osaka, Japan (private communication), which is in excellent agreement with ours. Sirakawa cites recovery of two chromatographic fractions, I and the aminotriazole, as evidence that the aminotriazole salt (not Heimbach's supposed amide, II) is the "trimolecular product" in reaction between diketene and 3-amino-1,2,4-triazole. He also prepared the salt by crystallization of a mixture of I and aminotriazole from a concentrated aqueous solution.

TABLE I

ULTRAVIOLET ABSORBANCE DATA FOR POLYAZAINDENES AND RELATED COMPOUNDS



Number	Compound	Substituent (s)	Absorbance Maxima[a] $\lambda_{max.}$ (mμ) and $\epsilon_{max.}$ ($\times 10^{-3}$) at *p*H~1	at *p*H~10
IV	1,2,3a,4-Tetrazaindene	5-Methyl, 7-oxo[b]	269 (7.1)	265 (4.7), 255 (4.3), 294 (11.5)
V	1,2,3a,4-Tetrazaindene	5-*p*-Anisyl, 7-oxo	253 (9.6)	258 (12.4), 308 (5.0)
VI	1,2,3a,7-Tetrazaindene	4-Methyl, 6-oxo	247 (6.5)	275 (2.4)
VII	1,2,3a,7-Tetrazaindene	6-Methyl, 4-oxo	288 (8.2)	253 (4.0), 300 (10.1)
VIII	1,3,3a,7-Tetrazaindene	4-Methyl, 6-oxo[c]	264 (6.7)	273 (4.0)
I	1,3,3a,7-Tetrazaindene	6-Methyl, 4-oxo	270 (11.4)	255 (6.6), 280 (12.1)
IX	1,3,3a,7-Tetrazaindene	2-Amino, 6-methyl, 4-oxo	270 (9.1)	282 (8.9)
X	1,3,3a,7-Tetrazaindene	2,6-Diamino, 4-oxo	277 (12.3)	272 (5.5)
XI	1,3,3a,7-Tetrazaindene	5-Ethyl, 6-methyl, 4-oxo	240 (4.7), 278 (11.4)	258 (6.4), 287 (12.3)
XII	1,3,3a,7-Tetrazaindene	5-Carbethoxy, 4-oxo	282 (10.7), 247 (8.2)	293 (14.6), 262 (8.8)
XIII	1,3,3a,7-Tetrazaindene	6-Methyl, 2-methylmercapto, 4-oxo	266 (12.9)	280 (10.3)
XIV	1,2,3,4,6-Pentazaindene	5,7-Dioxo	262 (7.0)	277 (6.1)
XV	1,2,3,4,6-Pentazaindene	5-Methyl, 7-oxo	253 (9.3)	257 (8.3)
XVI	1,2,3,4,6-Pentazaindene	5-Amino, 7-oxo	247 (8.1)	277 (5.9)
XVII	1,2,3,4,6-Pentazaindene	7-Amino, 5-mercapto, 2-(4-sulfophenyl)	257 (10.2), 335 (8.5)	252 (10.9), 256 (11 0)
XVIII	Benzo-1,2,3-triazole	—	262 (7.1)	274 (8.5)
XIX	Benzo-1,2,3-triazole	6-Chloro, 4-nitro	293 (6.1), 340 (5.9)	360 (6.5)
XX	2-Methyl-4-oxo-1,4a,9-triazafluorene	—	297 (6.1)	335 (8.4)

[a] Ultraviolet absorbance spectra for all compounds listed in Table I were recorded for dilute aqueous solutions containing either 20 mg. or 5×10^{-5} mole per liter, and converted to molar extinction curves for subsequent comparison. The *p*H was adjusted by adding one drop of concentrated hydrobromic acid per 3 ml. in the cuvette before recording the "acid curve" (*p*H 1.2) and then adding two drops of concentrated ammonium hydroxide to this solution before recording the "basic curve" (*p*H 9.6). Small variations in *p*H at either level appeared to have no effect on the curve. The ultraviolet measurements were made using 1-cm. silica cuvettes in a Cary recording spectrophotometer, Model 14 PM. [b] New light is shed here on the controversial structure of IV, the product of reaction between 4-amino-1,2,4-triazole and ethyl acetoacetate. The data in Table I show a general resemblance of IV and I and VII (both 4-ones) and a dissimilarity of IV to VI (a 6-one). The resemblance and dissimilarity are even more obvious in a comparison of the complete spectra. By implying that the position of the carbonyl is adjacent to the heterocyclic ring, rather than in the 5- or 6- position, these data support the structure that is given here for IV, notwithstanding the contrary opinion of Russian workers [A. N. Kost and F. Gents, *J. Gen. Chem. U.S.S.R.*, 28, English translation 2796–2801 (1958)]. [c] L. A. Williams, Part VIII, *J. Chem. Soc.*, 3046 (1961).

amino-1,2,4-triazole in 100 ml. of acetic acid was refluxed for 4 hr. The solution was evaporated to dryness *in vacuo* and the residue triturated with 25 ml. of absolute ethanol. The solid was collected and recrystallized from absolute ethanol to yield 13.5 g. of white solid, m.p. 195–197°. This compound gave a correct analysis for the aminotriazole salt of 5-carbethoxy-6-methyl-4-oxo-1,3,3a,7-tetrazaindene.

Anal. Calcd. for $C_{11}H_{14}N_8O_3$: C, 43.1; H, 4.6; N, 36.7. Found: C, 42.9; H, 4.4; N, 36.8.

Hydrolysis of this salt in 10% sodium hydroxide solution yielded 5-carboxy-6-methyl-4-oxo-1,3,3a,7-tetrazaindene, m.p. 212°, which was decarboxylated to give 6-methyl-4-oxo-1,3,3a,7-tetrazaindene, m.p. 278°. The ultraviolet absorbance curve of the latter compound was identical with an authentic sample of I.

Reaction of 3-amino-1,2,4-triazole with ethyl ethoxalylpropionate. A mixture of 4 g. (0.05 mole) of aminotriazole and 11 g. (0.05 mole) of ethyl ethoxalylpropionate in 100 ml. of ethanol was refluxed for 4 hr. After cooling, the solid was collected and recrystallized from aqueous dimethylformamide to yield 1.5 g. of material which gave an analysis corresponding to the aminotriazole salt of 6-carbethoxy-4-oxo-5-methyl-1,3,3a,7-tetrazaindene, m.p. 257–259°.

Anal. Calcd. for $C_{11}H_{14}N_8O_3$: C, 43.1; H, 4.6; N, 36.7. Found: C, 42.8; H, 4.6; N, 36.5.

If acetic acid was used as the reaction medium, the amide[8] from aminotriazole and the tetrazaindene was formed directly rather than the salt. Both were hydrolyzed in dilute acid to give the 5-methyl-4-oxo-1,3,3a,7-tetrazaindene.

Other salts. Equal molecular proportions of both components were dissolved, mixed, and recrystallized. For III, the solvent was *N,N*-dimethylformamide. The hydrazine salt was recrystallized from water, the secondary amine salt from acetonitrile, and the others from ethanol or aqueous methanol. Their properties are given in Table II.

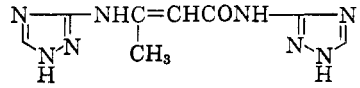
(8) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. Van Allan, *J. Org. Chem.*, 24, 793 (1959); esp. 794.

TABLE II

AMINE SALTS OF VARIOUS TETRAZAINDENES

Amine	Tetraza-indene	M.P.	Mol. Wt.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	λ_{max} ($\epsilon \times 10^{-3}$) at pH ~1	λ_{max} ($\epsilon \times 10^{-3}$) at pH ~10
n-Propylamine	I	165[a]	209	51.7	7.2	33.5	51.5	7.2	32.9	270 (11.1)	255 (6.3) 280 (11.7)
Diethylamine	I	160	223	53.4	7.6	31.4	53.3	7.4	31.8	270 (11.6)	255 (6.6) 280 (12.3)
Triethylamine	XII	138–140	309	54.2	7.4	—	54.0	7.2	—	282 (11.3) 247 (8.7)	293 (15.6) 262 (9.4)
Hydrazine	I	178–180	182	39.6	5.5	46.1	40.4	5.4	47.7	270 (11.8)	255 (6.8) 280 (12.4)
3-Amino-1,2,4-triazole[b]	I		234							270 (11.0)	255 (6.3) 280 (11.6)
3-Amino-5-methyl-1,2,4-triazole	[c]	238–240	278	43.2	5.0	40.4	43.2	5.0	40.8	270 (10.6)	255 (6.3) 280 (11.6)
3,5-Dimethylpiperidine	I	160	263	59.4	8.0	26.6	59.8	8.0	26.7	270 (11.3)	255 (6.4) 280 (12.0)
Morpholine	I	160	237	50.7	6.3	29.5	50.6	6.4	30.0	270 (11.1)	255 (6.4) 280 (11.9)

[a] M.p. 169–170° after recrystallization from benzene. [b] This salt was previously given the erroneous structure[6]:



[c] 2-Hydroxymethyl derivative of I (ref. 8, p. 745).

Acknowledgment. The authors are indebted to Mrs. E. M. Gordon for ultraviolet spectra, to Dr. D. W. Stewart and Miss T. J. Davis for infrared spectra, and to Dr. E. P. Przybylowicz for sublimation of the salt, III. The helpful interest and advice of Dr. C. F. H. Allen are acknowledged with gratitude.

ROCHESTER 4, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ARIZONA STATE UNIVERSITY]

Purine Nucleosides. II. The Preparation of 6-Substituted 9-(Tetrahydro-2-furyl)purines and 6-Substituted 9-(Tetrahydro-2-thienyl)purines as Models of Purine Deoxynucleosides[1,2]

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Received February 27, 1961

The reaction of 2,3-dihydrofuran or 2,3-dihydrothiophene with certain 6-substituted purines in the presence of acid has been shown to yield the corresponding 9-(tetrahydro-2-furyl)- or 9-(tetrahydro-2-thienyl)purine. This reaction provides a novel method of introducing a five-membered ring into position 9 of the purine ring. These derivatives are interesting models of purine deoxynucleosides, several of which possess significant antitumor activity against adenocarcinoma 755. As there are no hydroxyl groups present for *in vivo* phosphorylation, these compounds are interesting candidates for further biochemical study at the nucleoside level. The synthesis of 9-(tetrahydro-2-furyl)adenine (III), a model of deoxyadenosine, has been accomplished from 6-chloro-9-(tetrahydro-2-furyl)purine (I).

A program of synthesis of various purine derivatives as antitumor agents revealed that certain 9-alkyl-6-substituted purines such as 9-methyl-6-purinethiol[3] and 9-methyl-6-chloropurine[3] retained a considerable amount of the antitumor activity possessed by the parent 6-substituted purines. As the corresponding 7-methyl-6-purinethiol[4] and 7-methyl-6-chloropurine[4] were devoid of antitumor activity, it seemed possible that the 9-substituted purines might owe their activity to the structural relationship to purine nucleosides rather than to possible *in vivo* demethylation. As 6-chloro-9-phenylpurine[5] and 9-phenyl-6-purinethiol[5] exhibited no antitumor activity, an effort was made

(1) Supported by Contract SA-43-ph-1928 with the Cancer Chemotherapy National Service Center of the National Cancer Institute, National Institutes of Health.

(2) Presented in part before the Division of Organic Chemistry at the 138th Meeting of the American Chemical Society, September 1960, New York, N. Y.

(3) R. K. Robins and H. H. Lin, *J. Am. Chem. Soc.*, 79, 490 (1957).

(4) R. N. Prasad and R. K. Robins, *J. Am. Chem. Soc.*, 79, 6401 (1957).

(5) S. M. Greenberg, L. O. Ross, and R. K. Robins, *J. Org. Chem.*, 24, 1314 (1959).