Recrystallized from benzene, this gave yellow needles melting at 223–225°.

Anal. Calcd. for $C_{13}H_8BrClN_2$: C, 50.8; H, 2.62. Found: C, 50.9; H, 2.83.

c. *2,8-Bis(methylamino)-3-methylphenazine.* In a bomb tube was put a mixture of 0.88 g. recrystallized 2-bromo-8-chloro-3-methylphenazine, 4 cc. of a 40% aqueous solution of methylamine, and about 0.1 g. of cuprous chloride. The tube was sealed and heated about 20 hr. in a bomb oven at 170°. A very dark red solid resulted, which was extracted in a Soxhlet apparatus with a minimum of benzene, and the resulting solution put through a column of basic alumina 14 mm. in diameter by 140 mm. in length. Three zones resulted: a black layer on top, a dark red zone in the middle, and a lighter red zone on the bottom. The black portion was removed by spatula, and the bottom zone eluted with benzene. Soxhlet extraction of the middle dark red zone with ether, followed by evaporation of the latter, gave 0.1 g. of reddish-brown microcrystals. These melted, with gradual decomposition, at 205–210°. Because no good solvent for recrystallization was found, the product was analyzed directly.

Anal. Calcd. for $C_{15}H_{16}N_4$: C, 71.4; H, 6.39. Found: C, 71.6; H, 6.36.

This compound was dissolved in dilute hydrochloric acid, and the solution diluted to a concentration of 1 to 40,000 with Hank's basal salt solution, to provide a properly buffered saline medium for living cells. When the *p*H was adjusted to 7.2 by the addition of sodium hydroxide, the resultant solution stained Sarcoma 37 ascites tumor cells very well, in the same manner as is shown by neutral red, and with little indication of toxicity.

2-Methylamino-8-n-propylaminophenazine. (a) *2-Chloro-8-n-propylaminophenazine.* A mixture of 2.5 g. of 2,8-dichlorophenazine (recrystallized, and ground to pass an 80-mesh sieve), 2.5 g. of anhydrous sodium acetate, and 10 cc. of *n*-propylamine was heated for 24 hr. in a sealed tube, in a bomb oven at 195°. The contents of the tube were dried on the steam bath, and then put into benzene solution by Soxhlet extraction. Passage through a column of basic alumina 37 mm. in diameter by 165 mm. long gave three zones, plus a small black layer at the top. The product desired was in the middle zone, dark purple in color. This zone was mechanically separated, and exhausted by Soxhlet extraction with ether. Evaporation of the ether gave 1.16 g. of dark red product. When this was recrystallized from 75% methanol it formed orange-red microcrystals, melting at 190–191°.

Anal. Calcd. for $C_{15}H_{14}ClN_3$: C, 66.4; H, 5.16. Found: C, 66.5; H, 5.42.

(b) *2-Methylamino-8-n-propylaminophenazine.* An intimate mixture was made of 0.45 g. of recrystallized and finely ground 2-chloro-8-*n*-propylaminophenazine and 0.45 g. of anhydrous sodium acetate, and to this was added 10 cc. of a 40% solution of aqueous methylamine. The whole was sealed in a bomb tube, and heated for 16 hr. in a bomb furnace 174–178°. The same procedure as above gave three zones on basic alumina, plus a small dark upper band. Mechanical separation of the bottom, nearly black zone, followed by extraction of it with ether, and evaporation of the solvent, gave 0.12 g. of deep-red microcrystals, melting at 155–160°, with decomposition. This material resisted all attempts at recrystallization, and was hence analyzed directly.

Anal. Calcd. for $C_{16}H_{18}N_4$: C, 72.7; H, 6.80. Found: C, 72.3; H, 6.93.

This compound, when treated in the same manner as already detailed for 2,8-bis(methylamino)-3-methylphenazine, stained ascites tumor cells similarly.

2-Alkylamino-8-chlorophenazines. In general, these compounds were prepared by bomb tube reactions carried out as with the 2-chloro-8-*n*-propylaminophenazine already described, starting in all instances with 2,8-dichlorophenazine, recrystallized and ground to pass an 80-mesh screen. It was found, though, that the methyl- and ethylamines were so much more reactive than their higher homologs that replacement of the first chlorine of the 2,8-dichlorophenazine could be carried out at 100°, while the amines from propyl on up required a considerably higher temperature. The time required was not carefully determined, but was judged roughly by the appearance of the bomb tube contents as time went on. Elimination of the unused portion of the amine after the reaction's completion was carried out by washing with water for the amines up to *n*-amylamine, and by steam distillation for higher homologs. All separations were carried out by extracting the whole reaction mixture with benzene in a Soxhlet apparatus, chromatographing the resulting solutions on basic alumina, separating the darkest red zone mechanically, and isolating the product by extraction of this zone with ether. The crude 2-alkylamino-8-chlorophenazines were then recrystallized from *n*-heptane. It was found that sodium acetate gave better results than did ammonium acetate, cupric acetate, or no catalyst at all, and so a weight of sodium acetate equal to that of the 2,8-dichlorophenazine was arbitrarily taken when the dichloro compound was heated with the various primary amines. The following tables summarize the results. The first table gives the yields of crude products, and shows some variations in yield obtained by such changes in reactions conditions as different temperatures, different lengths of heating, and use of anhydrous or aqueous amine. All reactions with the same amine were marked by the same letter. The second table deals with the properties and analyses of the pure monoalkylamines.

BETHESDA 14, MD.

[COMMUNICATION NO. 2092 FROM THE KODAK RESEARCH LABORATORIES, EASTMAN KODAK CO.]

The Structure of Certain Polyazaindenes. VII. 4-Amino-6-methyl-1,3,3a,7-tetrazaindene and Its Derivatives[1a]

G. A. REYNOLDS AND J. A. VANALLAN

Received June 2, 1960

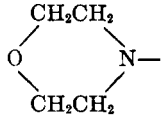
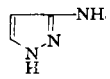
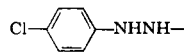
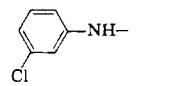
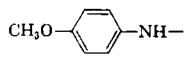
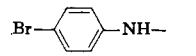
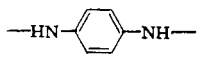
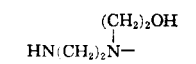
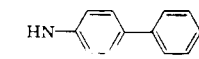
The synthesis of a number of new amino tetrazaindenes is described.

In connection with the determination of structure of some tetrazaindenes,[1b] we had occasion to synthesize a number of 4-aminotetrazaindenes. These amines were synthesized by reaction of 4-chloro-6-methyl-1,3,3a,7-tetrazaindene (I) and the

(1a) The name of J. A. VanAllan as co-author of Part V in this series [*J. Org. Chem.*, **25** 361 (1960)] was inadvertently omitted.

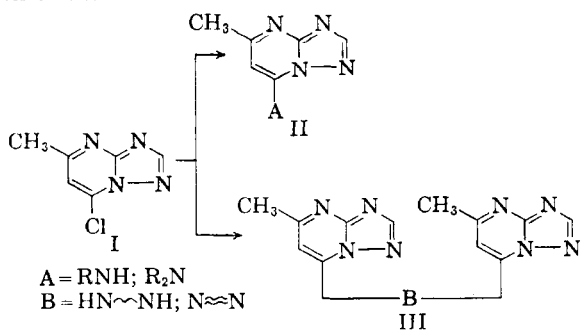
TABLE I

4-AMINO-1,3,3a,7-TETRAZAINDENES

	A;B	M.P.	Method of Preparation	Solvent for Recrystallization	Calcd., % C	H	N	Found, % C	H	N	Yield, %
IIa	C_2H_5NH—	147	B	Ethanol	54.2	6.2	39.6	54.6	6.1	39.6	94
IIb		162	A	Benzene-ligroin	54.8	5.9	31.9	55.2	6.2	31.7	96
IIc	C_6H_5NH—	188	C	Benzene	64.1	4.9	31.1	64.0	4.8	30.7	65
IId	$HClNH_2(CH_2)_2NH$—[a]	196–198	C	Benzene-ethanol	42.1	5.7		41.8	5.9		20
IIe	H_2NNH—	276–278	A	Ethanol	43.8	4.9	51.2	43.9	4.8	51.3	55
IIf	$CH_3C_6H_4SO_2NHNH$—	240	D	Ethanol	49.2	4.4		49.4	4.4		82
IIg		315	E	Dimethylformamide			51.8			51.5	61
IIh		265	C	Ethoxyethanol	55.5	3.9	27.0	55.1	4.2	27.1	93
IIi[b]		228	C	Ethanol	55.5	3.9	27.0	55.6	4.1	27.0	65
IIj		211	C	Ethanol	61.2	5.1	27.4	61.0	5.2	27.7	60
IIk		265	C	Ethanol	47.4	3.2	23.0	47.9	3.5	23.3	89
III	$C_{12}H_{25}NH$—	65	C	Benzene-ligroin	68.2	9.8	22.1	68.2	9.8	22.1	64
IIIa	$HN(CH_2)_2NH$[a]	330	C	Dimethylformamide	51.8	4.9		51.3	5.2		91
IIIb	$HN(CH_2)_6NH$	242	C	Ethanol	56.8	6.3		56.8	6.8		63
IIIc		325	C		54.8	5.1	40.1	54.5	5.5	40.2	91
IIId		236–238	C	Dimethylformamide	52.2	5.4	38.0	52.6	5.8	38.2	86
IIIe		305	C	Dimethylformamide	64.3	4.5	31.3	64.0	4.8	31.3	57

[a] IIIa separated from the reaction mixture on cooling and IId was obtained by evaporation of the reaction solvent. [b] *o*-Choroaniline failed to react by this procedure.

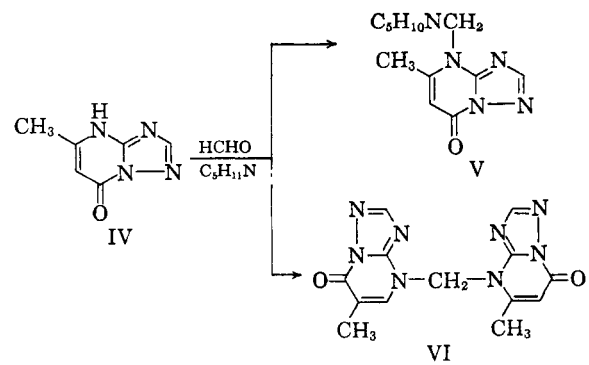
appropriate amine, as indicated below. The only anomaly was the reaction of asymmetrical dimethylhydrazine with I; this gave a product that had an analysis corresponding to 4-methylhydrazino-6-methyl-1,3,3a,7-tetrazaindene. The initial reaction was probably the quaternization of the dimethylhydrazine, followed by the elimination of methyl chloride.



(1b) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, 24, 792 (1959).

The physical properties, method of preparation, yield, and analytical data for these derivatives are collected in Table I.

With a view to obtaining amino derivatives of the tetraazaindene series in which the amino group is not directly attached to the ring, 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (IV) was treated with formaldehyde and piperidine. The two products of this reaction were assumed to be 6-methyl-7-



piperidinomethyl-4-keto-1,3,3a,7-tetrazaindene (V), and bis(6-methyl-4-oxo-1,3,3a,7-tetrazainden-7-yl)-methane (VI). The reaction was not investigated further.

EXPERIMENTAL

Method A. A mixture of 1 equivalent of 4-chloro-6-methyl-1,3,3a,7-tetrazaindene[1b] (I), 3 equivalents of the amine, and ten parts by volume of ethanol was refluxed for 2 hr., and then cooled. The solid was either collected or the reaction mixture evaporated to dryness, depending on the solubility of the product in ethanol.

Method B. It was carried out in the same manner as Method A except that the reactants were allowed to stand at room temperature for 2 hr., rather than being refluxed.

Method C. A mixture of 1 equivalent of I, 1 equivalent of the amine, and 1.5 equivalents of triethylamine in ten parts by volume of ethanol was refluxed 2 hr. and then evaporated to dryness.

Method D. Acetonitrile was employed in place of ethanol in Method A.

Method E. Equivalent amounts of I, amine, and sodium bicarbonate in seven parts by volume of nitrobenzene were refluxed 2 hr. and the solid was collected and washed with water and ether.

6-Methyl-7-piperidinomethyl-4-keto-1,3,3a,7-tetrazaindene. Piperidine (2.8 g.) was dissolved in 2.5 ml. of 40% formalin. After the exothermic reaction had subsided, 4.5 g. of 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (IV) was added, followed by the addition of 25 ml. of ethanol. After a 1-min. reflux, solution was complete; in 10 min., a white precipitate settled out. Reflux was continued for 30 min. more. After cooling, the product was collected and then crystallized from alcohol to give 4 g. of V, m.p. 230°.

Anal. Calcd. for $C_{12}H_{17}ON_5$: C, 58.2; H, 6.9. Found: C, 58.7; H, 6.9.

In one run, an insufficient quantity of piperidine was used and a product which had an analysis corresponding to bis(6-methyl-4-oxo-1,3,3a,7-tetrazainden-7-yl)methane (VI), m.p. 310°, was obtained.

Anal. Calcd. for $C_{13}H_{12}O_2N_8$: C, 50.0; H, 3.9; N, 35.9. Found: C, 50.5; H, 4.0; N, 35.7.

ROCHESTER 4, N. Y.

[CONTRIBUTION FROM THE DYSON-PERRINS LABORATORY]

Synthetic Furocoumarins. I. A New Synthesis of Methyl-substituted Psoralenes and Isopsoralenes

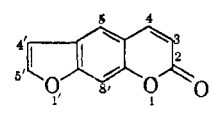
KURT D. KAUFMAN[1,2]

Received May 13, 1960

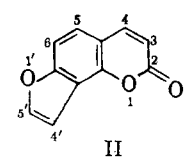
Three methyl-substituted psoralenes and two methyl-substituted isopsoralenes have been synthesized by a new method from *o*-allyl-7-hydroxycoumarins by acetylation, bromination, and cyclization in a basic medium. 7-Allyloxycoumarins undergo Claisen rearrangement to 8-allyl-7-hydroxycoumarins, which lead to methylated isopsoralenes. 7-Allyloxy-8-methylcoumarins rearrange to 6-allyl-7-hydroxy-8-methylcoumarins, which produce methylated psoralenes. 3-Allyloxyphenyl acetate gives a mixture of 2-allylresorcinol and 4-allylresorcinol on Claisen rearrangement followed by hydrolysis. The latter compound was converted to a dimethylpsoralene.

Naturally occurring furocoumarins have recently attracted attention because several of them alter the response of human skin to ultraviolet radiation.[3] In particular, xanthotoxin (8-methoxypsoralene) has been used clinically to prevent sun burning, to encourage sun tanning, and in the treatment of vitiligo.[3] Its effect on ultraviolet carcinogenesis has also been studied.[3,4] The erythema inducing activity of several synthetic furocoumarins has been studied in an effort to understand their biological mechanism of action.[5] The photosensitization of bacteria by a variety of furocoumarins (including some synthetic compounds) has also been reported.[6]

Several furocoumarin nomenclatures are currently in use and this has occasionally led to confusion.[7] Throughout this and later papers, structure I shall be designated psoralene and shall be numbered as shown, which is in accordance with the recommendation of the Food and Drug Administration.[7] Structure II shall be designated isopsoralene with a similar numbering system.[8]



I



II

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(2) This investigation was made possible by the interest and advice of Sir Robert Robinson and by the support provided by a Fulbright Grant administered by the United States Educational Commission in the United Kingdom.

(3) Psoralenes and radiant energy, proceedings of a symposium. *J. Invest. Dermatol.*, **32**, 131–391 (1959).

(4) M. A. O'Neal and A. C. Griffin, *Cancer Research*, **17**, 911 (1957).

(5) (a) M. A. Pathak and T. B. Fitzpatrick, *J. Invest. Dermatol.*, **32**, 255 and 509 (1959); M. A. Pathak, J. B. Fellman, and K. D. Kaufman, *ibid.*, **35**, 165 (1960); (b) L. Musajo, *Farmaco (Pavia) Ed. sci.*, **10**, 3 (1955); L. Musajo, G. Rodighiero, G. Caporale, and C. Antonello, *Farmaco (Pavia) Ed. sci.*, **13**, 355 (1958).

(6) W. L. Fowlks, D. G. Griffith, and E. L. Oginsky, *Nature*, **181**, 571 (1958).

(7) A. C. Curtis, *J. Invest. Dermatol.*, **32**, 133 (1959).

(8) *Chemical Abstracts* prefers δ-lactone of 6-hydroxy-5-benzofuranacrylic acid for I and δ-lactone of 4-hydroxy-5-benzofuranacrylic acid for II, but these names are not in common usage.