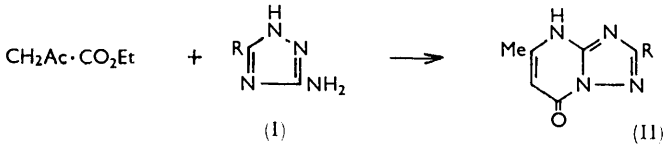
583. *The Structure of Certain Polyazaindenes. Part VIII.* Tetra-azaindenes derived from the Reaction of Ethyl β-Ethoxy-α-ethoxycarbonylcrotonate with 3-Amino-1,2,4-triazoles.*

By L. A. Williams.

The reaction of ethyl β-ethoxy-α-ethoxycarbonylcrotonate with 3-amino-1,2,4-triazoles can occur by two different routes, depending on the basicity of the medium. A number of tetra-azaindenes have been prepared by this reaction and their spectra compared.

3-Amino-1,2,4-triazole (I; R = H) and ethyl acetoacetate in acetic acid were shown by Bülow and Haas [1] to give a compound, m. p. 278°, which they formulated as the hydroxy-form of (II; R = H), although four isomeric structures for this compound are possible.

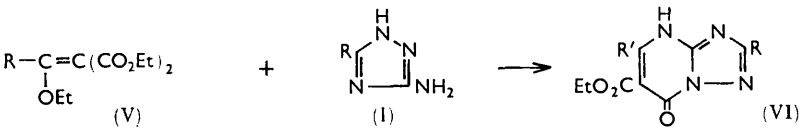


(I) (II)

Allen and his co-workers [2,3] later proved the structure (II) to be correct and prepared two further isomers (III; R = H) and (IV; R = H). They also showed [2] that 3-amino-1,2,4-triazole and ethyl β-ethoxy-α-ethoxycarbonylacrylate (V; R = H) in acetic acid or

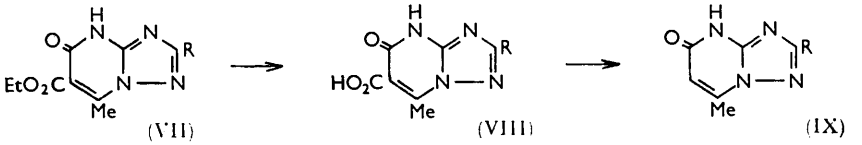
(III) (IV)

trichlorobenzene give a tetra-azaindene, to which they assigned, on the basis of its spectral characteristics, the structure (VI; R = R′ = H). Birr,[4] on the other hand, stated that the triazole (I; R = H) with ethyl β-ethoxy-α-ethoxycarbonylcrotonate (V; R = Me)



(V) (I) (VI)

gives a tetra-azaindene, to which he assigned structure (VII; R = H), which can be hydrolysed and decarboxylated to a compound isomeric with that obtained by Bülow and Haas. Reaction of the crotonate (V; R = Me) with the aminotriazole, like that described by Bülow and Haas, might give rise to four isomeric compounds. Birr gave neither details of his procedure nor proof of the structure of his product, and his proposed structure



(VII) (VIII) (IX)

is not that which might be expected by analogy with the work of Allen *et al.*[2] It, therefore, seemed desirable to examine the reaction further, and to compare the products with the three known isomers (II, III, and IV; R = H).

* Part VII, Reynolds and VanAllan, *J. Org. Chem.*, 1961, **26**, 115.

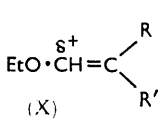
[1] Bülow and Haas, *Ber.*, 1909, **42**, 4638.
[2] Allen, Beilfuss, Burness, Reynolds, Tinker, and VanAllan, *J. Org. Chem.*, 1959, **24**, 779.
[3] Allen, Reynolds, Tinkers, Williams, and VanAllan, *J. Org. Chem.*, 1960, **25**, 361.
[4] Birr, *Z. wiss. Phot.*, 1952, **47**, No. 1—3, 2; see also Heimbach, B.P. 636,758.

Reaction of the triazole (I; R = H) with the crotonate (V; R = Me) in pyridine gave two isomeric esters. Only one of these formed a pyridinium salt, which was isolated by the addition of ether to the reaction mixture, and the free ester, m. p. 175°, was obtained by the acidification of an aqueous solution of this salt. The second ester, m. p. 208°, was obtained by chilling the ethereal filtrate. Both these esters were hydrolysed by 10% aqueous sodium hydroxide to acids, which were readily decarboxylated on melting or on boiling in quinoline or dimethylaniline. The ester, m. p. 175°, gives an acid, m. p. 212°, which on decarboxylation gives a compound, m. p. 278°, identified by mixed melting point and by ultraviolet and infrared absorption with the product of Bülow and Haas. This ester is, therefore, (VI; R = H, R′ = Me). The ester, m. p. 208°, on hydrolysis gives an acid, m. p. 228°, which, on decarboxylation, gives a compound, m. p. 266—267°, isomeric with that obtained by Bülow and Haas.

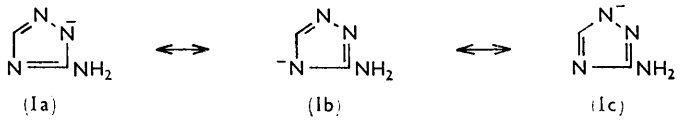
This compound differs from the isomers of (II) previously described in ultraviolet (Fig. 1) and infrared (Table 1) absorption and depresses their melting points.

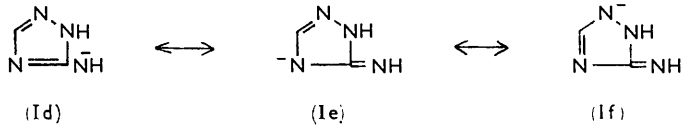
Since the structures of the isomers (II, III, and IV; R = H) have been established [3] the new compound must have structure (IX; R = H), while the 5-ethoxycarbonyl and 5-carboxy-derivatives are represented by (VII) and (VIII) respectively.

Reaction of the crotonate (V; R = Me) with the aminotriazole (I; R = H) is an electrophilic attack by the ester on the triazole ring. The ester contains three electrophilic centres and it is not known which of these first attacks the nucleophilic centres of the triazole. Diels *et al.*[5] have shown, however, that in the related α-cyano-β-ethoxyacrylonitrile (X; R = R′ = CN) and ethyl α-cyano-β-ethoxyacrylate (X; R = CN, R′ = CO_2Et) the electrophilic centre at the β-carbon atom is the point of attack by nucleophilic reagents in addition-elimination reactions, with the subsequent displacement of the alkoxy-group. Kamlet [6] has also shown that methyl β-ethoxy-α-nitroacrylate (X; R = NO_2, R′ = CO_2Me) behaves similarly. In the crotonate (V), therefore, it would be reasonable to expect that the electrophilic β-carbon atom would be the most reactive towards nucleophilic attack.


(X)

It is also not known which of the nucleophilic centres of the triazole is the most reactive. It would be expected, however, that this aminotriazole, which shows some acidic properties, would be more reactive as its anion, *i.e.*, under basic conditions. Such anions would be expected to be of the form (Ia ⟷ b ⟷ c) rather than (Id ⟷ e ⟷ f)

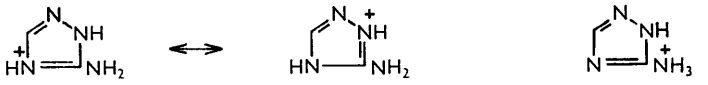

(Ia) (Ib) (Ic)


(Id) (Ie) (If)

since the aromatic resonance in the former is degenerate. If so, one would expect that the more reactive (β) electrophilic centre of the crotonate (V) would, under basic conditions, react with a cyclic nitrogen atom, rather than with the free amino-group, to give the ester (VII). On the other hand, under acidic conditions, the active triazole species, which is presumably a cation, would be expected to be (Ig ⟷ h), and not (Ii) because of the near-degenerate resonance stabilisation of the former. Consequently, under acid conditions, the primary amino-group would be expected to be the most reactive nucleophilic centre.

[5] Diels, Gartner, Kaack, *Ber.*, 1922, **55**, 3439.
[6] Kamlet, *J. Org. Chem.*, 1959, **24**, 714.

Irrespective of the nature of the more reactive electrophilic centre of the crotonate (V) it should, therefore, be possible to direct the attack on the triazole by the use of alkaline or acid conditions. The use of more strongly basic conditions than those given by pyridine as a solvent should favour even more strongly the formation of one of the isomeric esters.

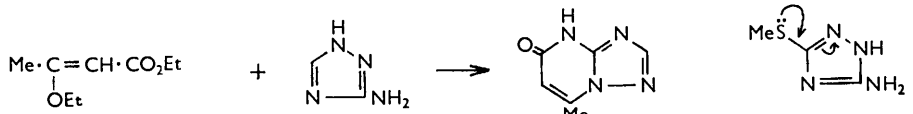


(Ig) (Ih) (Ii)

Indeed, the crotonate (V; R = Me) was found to react with the triazole (I; R = H) in alcohol in the presence of one equivalent of sodium ethoxide to give exclusively the ester (VII). In acidic conditions it would be expected that aminotriazole and the crotonate (V; R = Me) would give the ester (VI; R = H, R′ = Me), m. p. 175°. This was found to be the case, and apart from a small quantity of the acetyl derivative of the triazole (I) no other recognisable product was obtained.

From the above findings it can be concluded that in alkaline conditions the most highly nucleophilic centre in the triazole (I) is the $N_{(2)}$ atom.

The compound (III; R = H) is converted into its isomer (II; R = H) when heated in formic acid [7,8] or fused.[8] That no such isomerisation occurs during the decarboxylation of the acid (VIII; R = H) is established by the reaction of aminotriazole with ethyl β-ethoxycrotonate [9] (XI) in alcohol in the presence of an equivalent of sodium ethoxide, the compound (IX; R = H) being obtained. On the other hand, aminotriazole and the ethoxycrotonate (XI) react smoothly in acetic acid, to give only the compound (II; R = H).



(XI) (IX) (XII)

This sequence has been extended to reaction of the triazoles (I; R = SMe and NH_2) with the crotonate (V; R = Me), where it has been found that, in pyridine, the triazole I; R = SMe) reacts to give only the ester (VI; R = SMe; R′ = Me). This, if the above theory is correct, is to be expected since the $-M$ effect of the sulphur atom will decrease the acidity of the nucleus and thus make the formation of the anion (Ia) more difficult (cf. XII). In strongly basic conditions (sodium ethoxide) these two triazoles give the esters (VII; R = SMe and NH_2); these, after hydrolysis and decarboxylation, give the compounds (IX; R = SMe and NH_2) which are isomeric with those obtained by Fry.[10,11] The product of the condensation of the triazole (I; R = SMe) with ethyl acetoacetate in acetic acid was shown by Williams [12] to have structure (II; R = SMe). Two other isomers (III and IV; R = SMe) have been described by Allen *et al.*[3] The compound (IX; R = SMe), therefore, is the fourth of the isomers theoretically obtainable by the reaction described by Fry.

Spectrally these compounds show important similarities and differences. In the infrared region of the spectrum (Table 1) the findings of Allen *et al.*[2] that in the 6-oxo-compounds (IV; R = H and Me) the absorption band due to the amide-carbonyl group is at lower frequencies than for the isomers (II and III; R = H and Me), is confirmed for

[7] Allen, Beilfuss, Burness, Reynolds, Tinker, and VanAllan, *J. Org. Chem.*, 1959, **24**, 787.
[8] Shirakawa, *J. Pharm. Soc. Japan.*, 1958, **78**, 1395.
[9] Claisen, *Ber.*, 1895, **26**, 2731.
[10] Fry, B.P. 648,185.
[11] Fry, B.P. 648,184.
[12] Williams, *J.*, 1960, 1829.

compound (IX; R = H). In addition, the 4-oxotetra-azaindenes (II and III; R = H, SMe, and Me) differ from the 6-oxo-isomers (IV and IX) in showing an extra absorption band in the region of 1563—1575 cm.$^{-1}$ (Table 1) (see Allen *et al.*[2] for R = Me).

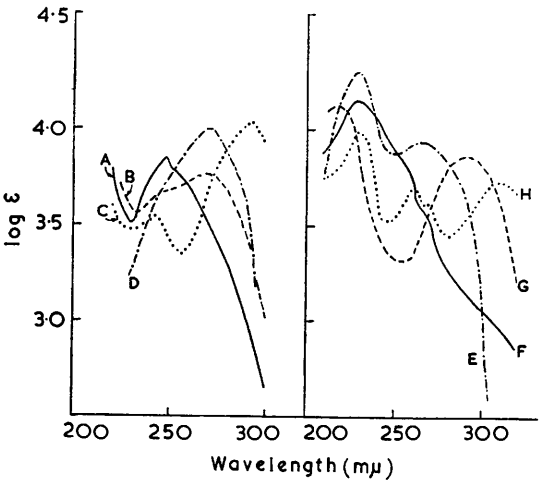
Further, the 1,3,3a,7-tetra-azaindenes are distinguished by a strong absorption band at 1325 cm.$^{-1}$ which is absent in the 1,2,3a,7-tetra-azaindenes. For the isomers (II and IX; R = SMe) this band, while still present, is less well developed.

TABLE 1. *Infrared absorption frequencies* (cm.$^{-1}$).

Compound	R	$\lambda_{max.}$	Compound	R	$\lambda_{max.}$	Compound	R	$\lambda_{max.}$	Compound	R	$\lambda_{max.}$
II	H	1695, 1600, 1563 (s)	II	SMe	1667, 1626, 1563 (s)	IX	H	1667, 1587 (s)	IX	SMe	1695, 1582 (s)
		1325 ms			1325 m			1325 s			1325 m
III	H	1724, 1626, 1575 (s)	III	SMe	1709, 1639, 1575 (s)	IV	H	1681, 1600 (s)	IV	SMe	1685, 1600 (s)

The ultraviolet absorption properties of the isomers (III and IV; R = H) in methanol and that of the isomer (II; R = H) in ammoniacal methanol have been described by Allen *et al.*[2,3] The absorptions of these compounds in methanol, together with that of the isomer (IX; R = H), are shown in Fig. 1, from which it is apparent that the 6-oxotetra-azaindenes absorb at lower extinction values than their 4-oxo-isomers. This is also the

FIG. 1. FIG. 2.



Ultraviolet absorption spectra of:

A, Compound IV, R = H. B, Compound IX, R = H. C, Compound III, R = H. D, Compound II, R = H. E, Compound II, R = SMe. F, Compound IV, R = SMe. G, Compound IX, R = SMe. H, Compound III, R = SMe.

case with the corresponding alkylthio-derivatives (Fig. 2). This is in agreement with Mason's findings [13] that with " nitrogen-containing heteroaromatic compounds containing two fused rings, *ortho*- and *para*-quinonoid conjugated systems may be qualitatively distinguished by the greater intensity of absorption in the long-wavelength band of the spectrum of the latter."

[13] Mason, *Chem. Soc. Special Publ.*, No. 3, p. 139.

Allen *et al.* have shown that for 4-oxotetra-azaindenes the absorption of the long-wavelength band of the 1,2,3a,7-isomers is bathochromically displaced relative to the 1,3,3a,7-isomer. In the 6-oxo-series, however, the reverse situation prevails with the 1,3,3a,7-isomers absorbing at considerably the longer wavelengths.

Further, for compounds (II), as the electropositive nature of R increases, the position and extinction value of the long-wavelength band is only slightly affected, while with the isomers (IX) there is a pronounced bathochromic shift. Allen *et al.*[2] found a similar shift with the ester (VI; R = R′ = H).

The structures assigned to isomers (II, III, IV, and IX; R = H) are further supported by their nuclear magnetic resonance properties although the differences involved are rather small. The spectra (see Table 2) were determined at 56·4 Mc. in pyridine solutions (*ca.* 1%), with tetramethylsilane as an internal reference. The line positions given are

TABLE 2. *Nuclear magnetic resonance peaks.*

Compound	II	III	IX	IV
τ	7·69	7·69	7·57	7·63
J	0·7	—	1·1	1·1

τ values. Compounds (IX) and (IV) have the methyl group close to the five-membered ring and in each case the absorption is at slightly lower fields than for the isomers (II) and (III). This almost certainly reflects partial aromatic character of the five-membered ring.[13] The fact that the methyl peak for compound (IX) is slightly lower than for compound (IV) may be due to the proximity of the second nitrogen atom.

The coupling constants are probably characteristic of six-membered ring types (*i.e.*, 2-pyridone or 4-pyridone); the insolubility of the compound (III) prevented resolution of the doublet and hence J could not be measured.

A final point is that the 1,3,3a,7-tetra-azaindenes are stronger acids than the 1,2,3a,7-isomers. In the series (R = H) the 4-oxo-compounds are stronger acids than the 6-oxo-isomers (Table 3).

TABLE 3. *Acid strengths.*

Substance	R	10^7K_a at 20°	R	10^7K_a at 20°	Substance	R	10^7K_a at 20°	R	10^7K_a at 20°
II	H	5·8	SMe	5·3	IX	H	1·7	SMe	3·3
III	H	2·4	SMe	1·1	IV	H	1·3	SMe	1·4

EXPERIMENTAL

Ultraviolet absorptions are for methanol solutions; infrared measurements were made on potassium bromide discs; analyses are by Mr. C. B. Dennis.

Ethyl β-Ethoxy-α-ethoxycarbonylcrotonate (*Ethoxyethylidenemalonate*) (V; R = Me).—Ethyl orthoacetate (324 g., 2 mol.), ethyl malonate (320 g., 2 mol.), and sodium (2·3 g., dissolved in ethanol, 60 c.c.) were heated together in an oil-bath. The temperature was raised during 30—45 min. to 170° by which time alcohol began to distil; it was collected after fractionation through a short column. Heating was continued and the temperature raised as necessary to maintain distillation of the alcohol. After about 4 hr. (bath-temperature 205°) distillation of alcohol ceased (300 c.c. collected). The mixture was allowed to cool to 80°, a vacuum was applied, and heating was recommenced. A small fore-run (b. p. below 96/2 mm.) was obtained and discarded; the crude product was collected at 96—130°/2 mm. This fraction was re-distilled and the fraction boiling at 96—98°/2 mm. was collected and was purified further as described by McElvain and Burkett,[15] to give 220 g. of crystals, m. p. 25—27°, n^{20} 1·463 (Found: C, 57·5; H, 8·1. Calc. for $C_{11}H_{18}O_5$: C, 57·4; H, 7·8%).

Ethyl 4,7-Dihydro-6-methyl-4-oxo-1,3,3a,7-tetra-azaindene-5-carboxylate (VI; R′ = Me).—(1) 3-Amino-1,2,4-triazole (I; R = H) (4·2 g.) and ethyl β-ethoxy-α-ethoxycarbonylcrotonate (11·5 g.) were refluxed together in pyridine (30 c.c.) for 16 hr. After cooling, ether (90 c.c.) was added, and the mixture was shaken for about 2 min. The precipitate, a pyridinium salt, was collected and dissolved in cold water and filtered. The clear solution was acidified and the

[14] Elvidge and Jackman, *J.*, 1961, 859.
[15] McElvain and Burkett, *J. Amer. Chem. Soc.*, 1942, **64**, 1831.

solid collected and recrystallised from water and charcoal to give the *tetra-azaindene* (2 g.), m. p. 175° (Found: C, 48·3; H, 4·9; N, 25·6. $C_9H_{10}N_4O_3$ requires C, 48·6; H, 4·5; N, 25·3%).

(2) The triazole (I; R = H) (21 g.) and ester (V; R = Me) (57·5 g.) were heated in acetic acid (40 c.c.) for 3 hr. On cooling, a gelatinous precipitate was obtained, which, after trituration with ether, solidified. This was recrystallised from alcohol and then water, the filtrate being acidified with hydrochloric acid to give 23 g. of product, m. p. 175°.

Ethyl 6,7-Dihydro-4-methyl-6-oxo-1,3,3a,7-tetra-azaindene-5-carboxylate (VII).—(1) The ethereal filtrate obtained after removal of the pyridinium salt in method (1) above was chilled to 4° and after 3—4 hr. the *ester* was collected and recrystallised from water (charcoal); it had m. p. 208° (3 g.) (Found: C, 48·5; H, 4·9; N, 25·4%).

(2) The above reaction was repeated but including triethylamine (5 g., 1 mol.), and the mixture was refluxed overnight. After cooling, ether (60 c.c.) was added, and the solution chilled, to give ultimately the ester (VII) (4 g.), m. p. 208°.

(3) To sodium (4·6 g.) dissolved in alcohol (120 c.c.) 3-amino-1,2,4-triazole (16·8 g.) and ethyl β-ethoxy-α-ethoxycarbonylcrotonate (46 g.) were added. The mixture was refluxed for 6 hr., after which water (120 c.c.) was added. The solution was cooled rapidly and acidified with concentrated hydrochloric acid. The product (VII) was collected and recrystallised from water; it had m. p. 208° (26 g.).

4,7-Dihydro-6-methyl-4-oxo-1,3,3a,7-tetra-azaindene-5-carboxylic Acid.—The ester (VI; R′ = Me) (2 g.) was refluxed for 1 hr. in 10% aqueous sodium hydroxide (20 c.c.). After cooling, the solution was acidified with concentrated hydrochloric acid and chilled. The precipitated *acid* (1 g.), recrystallised from water, had m. p. 212° with evolution of carbon dioxide. The melt re-solidified and melted again without gas evolution at 278° (Found: C, 41·2; H, 3·5; N, 27·3. $C_7H_6N_4O_3,0{\cdot}5H_2O$ requires C, 41·4; H, 3·5; N, 27·5%. A redried sample gave N, 28·9. $C_7H_6N_4O_3$ requires N, 28·9%).

6,7-Dihydro-4-methyl-6-oxo-1,3,3a,7-tetra-azaindene-5-carboxylic Acid (VIII).—The ester (VII) (26 g.), hydrolysed as above, gave the *acid* (21 g.) (from water), m. p. 228—229° (evolution of carbon dioxide), re-solidified, remelted at 266—267° (Found: C, 43·6; H, 3·4; N, 29·7%).

6,7-Dihydro-4-methyl-6-oxo-1,3,3a,7-tetra-azaindene (IX).—(1) The acid (VIII) (5 g.) was melted under a vacuum at 280° with evolution of carbon dioxide, and the *product* sublimed into a short air-condenser. It (3 g.) recrystallised from water as plates, m. p. 266—267° (Found: C, 47·8; H, 4·1; N, 37·5. $C_6H_6N_4O$ requires C, 48·0; H, 4·0; N, 37·3%), $\lambda_{max.}$ 270 mμ (log ε 3·75).

(2) Ethyl β-ethoxycrotonate [9] (15·8 g.) was added to alcohol (100 c.c.) in which sodium (2·3 g.) had been dissolved then 3-amino-1,2,4-triazole (8·4 g.) was added. The mixture was refluxed for 24 hr., then water (100 c.c.) was added and the solution acidified and chilled to give the product (2·2 g.), as plates, m. p. and mixed m. p. 266—267°.

Ethyl β-ethoxycrotonate (15·8 g.) and 3-amino-1,2,4-triazole (8·4 g.) were refluxed together in glacial acetic acid (100 c.c.) for 4 hr. On chilling to 15° the product (10 g.) separated. Recrystallised from water, it melted at 278°, alone or mixed with the compound (II; R = H) prepared by the method of Bülow and Haas.[1]

Ethyl 6,7-Dihydro-4-methyl-2-methylthio-6-oxo-1,3,3a,7-tetra-azaindene-5-carboxylate.—To sodium (2·3 g.), dissolved in alcohol (60 c.c.), ethyl β-ethoxy-α-ethoxycarbonylcrotonate (23 g.) and 3-amino-5-methylthio-1,2,4-triazole (I; R = SMe) (13·0 g.) were added. The mixture was refluxed for 1·5 hr. by which time the whole had solidified. Water (60 c.c.) was added and the solution cooled and acidified with concentrated hydrochloric acid. The *ester* that crystallised was recrystallised from 50% acetic acid, forming needles, m. p. 214° (12 g.) (Found: C, 44·3; H, 4·6; N, 20·3; S, 11·9. $C_{10}H_{12}N_4O_3S$ requires C, 44·7; H, 4·8; N, 20·9; S, 11·9%).

This ester was hydrolysed as above to the *acid*, m. p. 235° (from water) (Found: C, 39·9; H, 3·6; N, 23·7; S, 13·3. $C_8H_8N_4O_3S$ requires C, 39·9; H, 3·7; N, 23·2; S, 13·3%).

6,7-Dihydro-4-methyl-2-methylthio-6-oxo-1,3,3a,7-tetra-azaindene.—The preceding acid was heated under a vacuum until the evolution of carbon dioxide ceased. The *product* recrystallised from water as needles, m. p. 280—281°, depressed to 234° on admixture with its isomers described by Fry [10] and Allen *et al.*[3] (Found: C, 42·2; H, 4·3; N, 28·9; S, 16·3. $C_7H_8N_4OS$ requires C, 42·6; H, 4·6; N, 28·4; S, 16·3%); it had $\lambda_{max.}$ 292 mμ (log ε 3·97).

Ethyl 4,7-Dihydro-6-methyl-2-methylthio-4-oxo-1,3,3a,7-tetra-azaindene-5-carboxylate.—3-Amino-5-methylthio-1,2,4-triazole (3·8 g.) and ethyl β-ethoxy-α-ethoxycarbonylcrotonate (6·8 g.) were refluxed together in pyridine (30 c.c.) for 4 hr. After cooling, ether (120 c.c.) was

added and the mixture was chilled. The pyridinium salt which separated was collected and dissolved in water, and the solution was acidified. The *product* (1 g.) was collected and recrystallised from water as needles, m. p. 238° (0·75 g.) (Found: C, 44·5; H, 5·0; N, 21·5; S, 11·4%).

Ethyl 2-Amino-6,7-dihydro-4-methyl-6-oxo-1,3,3a,7-tetra-azaindene-5-carboxylate.—3,5-Diamino-1,2,4-triazole [16] (9·9 g.) and ethyl β-ethoxy-α-ethoxycarbonylcrotonate (23·0 g.) were refluxed in ethanol (60 c.c.) in which sodium (2·3 g.) had been dissolved. After 3—3·5 hr. water (60 c.c.) was added and the solution acidified. The solid *ester* (5 g.) was collected and recrystallised from water as needles, m. p. >300° (Found: C, 45·2; H, 4·7; N, 29·9. $C_9H_{11}N_5O_3$ requires C, 45·5; H, 4·6; N, 29·6%).

Hydrolysis as above gave an *acid* which, after suspension in boiling water to remove inorganic impurities, had m. p. >360° (Found: C, 40·0; H, 3·5; N, 33·5. $C_7H_7N_5O_3$ requires C, 40·2; H, 3·4; N, 33·5%).

2-Amino-6,7-dihydro-4-methyl-6-oxo-1,3,3a,7-tetra-azaindene.—The preceding amino-acid (1·5 g.) was heated under a vacuum until all had sublimed into a short air-condenser (the starting material did not melt previously). The *product* was collected and recrystallised from water as needles (0·9 g.), m. p. 357° (Found: C, 43·3; H, 4·4; N, 42·9. $C_6H_7N_5O$ requires C, 43·6; H, 4·2; N, 42·4%), $\lambda_{max.}$ 301 mμ (log ε 3·91).

The author thanks Messrs. B. S. Goode and I. Degan for the ultraviolet and infrared absorption measurements, Mr. J. H. Bridger for dissociation constants, Dr. E. B. Knott for helpful discussion, and Dr. L. M. Jackman for measurements and interpretation of the nuclear magnetic resonance spectra.

RESEARCH LABORATORIES, KODAK LIMITED,
HARROW, MIDDLESEX.

[*Received, November 18th*, 1960.]

[16] Hofmann and Ehrhart, *Ber.*, 1912, **45**, 2731.