428. *The Structure of Certain Polyazaindenes. Part X.* The Reaction of Ethyl α-Cyano(and α-Ethoxycarbonyl)-β-ethoxyacrylate and -β-ethoxycrotonate with Some α-Aminoazoles.*

By L. A. Williams.

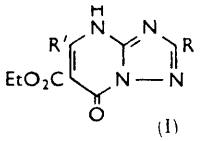
The reactions of ethyl α-cyano(and α-ethoxycarbonyl)-β-ethoxyacrylate and ethyl α-cyano-β-ethoxycrotonate with 3-amino-1,2,4-triazoles and 2-aminoimidazoline have been investigated. A number of new heterocyclic compounds have been prepared; their structures are discussed.

In a previous paper [1] it was shown that ethyl β-ethoxy-α-ethoxycarbonylcrotonate with 3-amino-1,2,4-triazoles in acid or basic media gives 4- (I; R′ = Me) or 6-oxo-1,3,3a,7-tetra-azaindenes (II; R′ = Me). Heimbach [2] states that ethyl β-ethoxy-α-ethoxycarbonylacrylate (III; R = H) and 3-amino-1,2,4-triazole in acetic acid give ethyl 6,7-dihydro-6-oxo-1,3,3a,7-tetra-azaindene-5-carboxylate (II; R = R′ = H), but Allen *et al.*[3] have

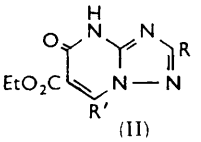
* Part IX, Hill, Reynolds, Tinker, and VanAllan *J. Org. Chem.*, 1961, **26**, 3836.

[1] Williams, *J.*, 1961, 3046.
[2] Heimbach, B.P. 636,758.
[3] Allen, Beilfuss, Burness, Reynolds, Tinker, and VanAllan, *J. Org. Chem.*, 1959, **24**, 779; cf. Reynolds and Sagal, U.S.P. 2,756,147.

shown that in acetic acid the 4-oxotetra-azaindene (I; R = R′ = H) results. The reaction of the acrylate (III; R = H) with 3-amino-1,2,4-triazole in alcohol in the presence of an equivalent of sodium ethoxide gave, unexpectedly, a product, m. p. 252°, identical with that obtained from the acid condensation.

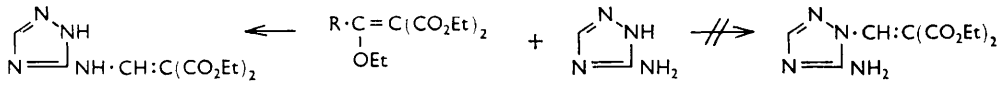


(I)



(II)

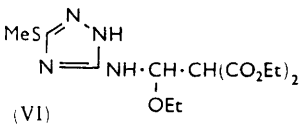
These reactions were repeated with 3-amino-5-methylthio-1,2,4-triazole. The product, m. p. 309—310°, of the acid condensation had the same absorption spectrum as the compound shown by Allen *et al.*[3] to be the ester (I; R = SMe, R′ = H). This reaction, in the presence of sodium ethoxide, gave a mixture of two isomeric esters, separable by their differing solubilities in water. The less soluble was the previous ester, m. p. 309—310°, which therefore has the structure (I; R = SMe, R′ = H). The more soluble has infrared absorption characteristic of 6-oxotetra-azaindenes[1] and, on the basis of its spectral characteristics, is regarded as having structure (II; R = SMe, R′ = H).



(V) (III) (IV)

Reaction at room temperature of the acrylate (III; R = H) with 3-amino-1,2,4-triazole in aqueous alcohol has also been described by Heimbach and Kelly,[4] who regard the product as the aminotriazolylmethylenemalonate (IV), though they give no evidence for this structure and record no physical properties of the product. If this structure is correct it should be possible to diazotize the amino-group and obtain dyes; and cyclization should lead to a 6-oxotetra-azaindene. In our hands, however, the compound could not be diazotized and coupled, and cyclization in refluxing acetic acid led to the known ester (I; R = R′ = H).[3] We conclude that structure (IV) is incorrect and that this compound is ethyl α-(1,2,4-triazol-3-ylamino)methylenemalonate (V), *i.e.*, that reaction occurs between the β-carbon atom of the acrylate (III; R = H) and the amino-group.

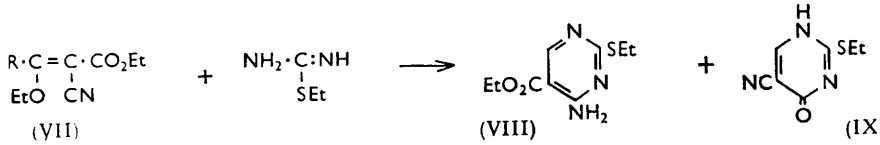
The same reaction, carried out at room temperature, with 3-amino-5-methylthio-1,2,4-triazole does not give a product analogous to (V), as the addition of the triazole to the β-carbon atom of the ester (III) is not followed by the elimination of alcohol. The monocyclic product (VI) is isolated; it is converted into the ester (I; R = SMe, R′ = H) by refluxing it in acetic acid.



(VI)

Attempts to effect reaction of ethyl β-ethoxy-α-ethoxycarbonylcrotonate (III; R = Me) with 3-aminotriazole in aqueous alcohol at room temperature were unsuccessful, but in the presence of sodium ethoxide reaction occurred, giving, as expected, the previously known ester (II; R = H, R′ = Me).[1]

In the above products of cyclization, there is no ambiguity in the nature of the groups present, as reaction occurs only between the β-ethoxy-group and one of the ethoxycarbonyl

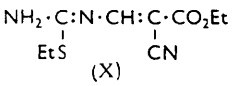


(VII) (VIII) (IX)

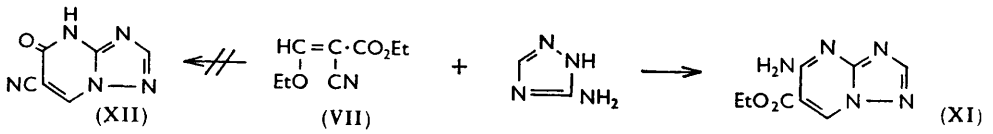
groups of the ester (III). However, replacing one of the ester groups by another reactive grouping allows the possibility of alternative modes of cyclization. For instance, Diels

[4] Heimbach and Kelly, U.S.P. 2,449,226.

et al.[5] have shown that reaction of ethyl α-cyano-β-ethoxyacrylate (VII; R = H) with monofunctional amines, such as benzylamine in alcohol, involves the β-ethoxy- and not the ethoxycarbonyl group. With difunctional reagents a number of products are possible; the cyanoacrylate (VII; R = H) has been shown by Johnson [6] to react with *S*-ethylisothiourea in the presence of alkali to give ethyl 4-amino-2-ethylthiopyrimidine-5-carboxylate (VIII) and 5-cyano-2-ethylthio-1,4-dihydro-4-oxopyrimidine (IX). In the absence of alkali only the aminopyrimidine (VIII) and the open-chain compound (X) are isolated.


(X)

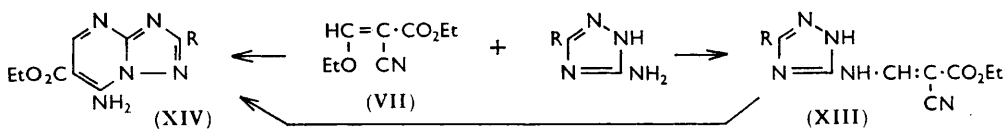
More recently De Cat and Van Dormael [7] obtained from the cyanoacrylate (VII) and 3-amino-1,2,4-triazole in the absence of a solvent a compound $C_8H_9N_5O_2$, m. p. 199—201°, which they believed to be the tetra-azaindene (XI), but they gave no evidence in favour of this structure. The possibility of cyclization to compound (XII) was excluded by the analyses. Repetition of this reaction * gave a compound of the stated formula, with m. p. 204—206°. However, the same reactants in acetic acid gave an isomeric compound, m. p. 224—225°. The infrared absorption spectrum of the product of the fusion reaction showed a strong band at 2222 cm.$^{-1}$ due [8] to a conjugated nitrile group; the product of the acid condensation showed no absorption in this region.


(XII) (VII) (XI)

3-Amino-5-methylthio-1,2,4-triazole and the cyanoacrylate (VII) gave a similar pair of isomers, only that formed by fusion showing nitrile absorption (2222 cm.$^{-1}$).

Since the products obtained from the fusion reactions are nitriles and analyses exclude the azaindene structure (XII), they must be triazolyl derivatives of the acrylate. This had not previously been considered; in conformity with it, they cyclised when refluxed in acetic acid, giving the (isomeric) products of the acid condensations. Various structures are then possible, depending on whether the fusion reaction involves the β-carbon atom or the ethoxycarbonyl group of the acrylate, and on the relative nucleophilic activity of the nitrogen atoms of the aminotriazoles. Reaction at the ester group is excluded since the products contain this group intact; in conformity are the findings of Diels *et al.*[5] and De Bollemont [9] that the acrylate (VII) reacts with amines initially at the β-atom. The amino-group, however, is no longer primary in the fusion product, since this cannot be diazotized. De Cat and Van Dormael's product is therefore the triazol-3-ylaminoacrylate (XIII). Such compounds would cyclize to 4- and not 6-aminotetra-azaindenes as assumed by De Cat and Van Dormael.[7]

Cyclization to the tetra-azaindene might involve either the $N_{(2)}$ or the $N_{(4)}$ atom of the ring, but it has been shown by the present author [10] that in acetic acid it is the $N_{(2)}$ atom

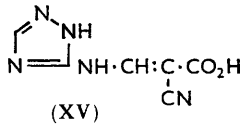

(XIV) (VII) (XIII)

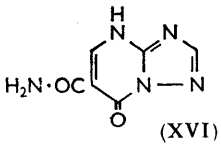
which is the centre of electrophilic attack, from which it follows that the products of the acid condensation have structures (XIV; R = H and SMe).

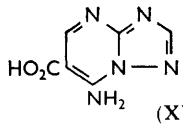
* In the absence of full experimental details it was assumed the reactants were fused together.

[5] Diels, Gartner, and Kaack, *Ber.*, 1922, **55**, 3439.
[6] Johnson, *Amer. Chem. J.*, 1909, **42**, 505.
[7] De Cat and Van Dormael, *Bull. Soc. chim. belges*, 1951, **60**, 69.
[8] Cf. Kitson and Griffiths, *Analyt. Chem.*, 1952, **24**, 334.
[9] De Bollemont, *Bull. Soc. chim. France*, 1901, **25**, 44.
[10] Williams, *J.*, 1960, 1829.

Johnson [6] has shown that the thioisoureido-acrylate (X) is converted quantitatively into the cyanopyrimidine (IX) in warm aqueous alkali. Cyclization of the triazolyl-acrylate (XIII; R = H) in 3N-aqueous sodium hydroxide at 100° for 3 min. gives a product which from its analysis ($C_6H_5N_5O_2$) might have structure (XV), (XVI), or (XVII). The first of these is eliminated since this product shows no nitrile band in its infrared absorption spectrum. Selection of (XVII) rather than (XVI) followed when it was found that the product was also obtained by alkaline hydrolysis of the ester (XIV; R = H).

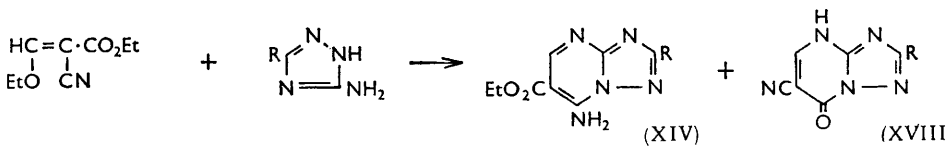

(XV)


(XVI)

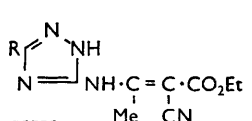

(XVII)

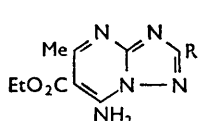
In the presence of sodium ethoxide in alcohol, the ester (XIII; R = H) cyclizes, giving a mixture of the amino-ester (XIV) with a small quantity of 5-cyano-4,7-dihydro-4-oxo-1,3,3a,7-tetra-azaindene (XVIII). This isolation of a cyanoazaindene establishes beyond doubt that De Cat and Van Dormael's product is a triazole derivative of the cyanoacrylate (VII), and not an aminoazaindene such as (XI) or (XIV).

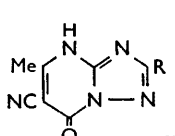
When 3-amino-1,2,4-triazole or its 2-methylthio-derivative and the cyanoacrylate (VII; R = H) react in alcohol in the presence of an equivalent of sodium ethoxide, a mixture of two products is obtained in each case, that are separable by means of sodium carbonate solution. The carbonate-insoluble components are the amino-esters (XIV; R = H and SMe); the second components each contain a cyano-substituent ($\nu_{max.}$ 2230 cm.$^{-1}$) and are identical with the cyano-compounds obtained by the action of sodium ethoxide on the esters (XIII; R = H or SMe) and are thus believed to have structures (XVIII; R = H or SMe), which are in line also with their spectral characteristics.[1]


(XIV) (XVIII)

Similar reactions were then carried out with ethyl α-cyano-β-ethoxycrotonate (VII; R = Me) and aminotriazoles (R = H, SMe, and NH_2). By analogy, it was expected that fusion in the absence of a solvent would give a crotonate (XIX; R = H, SMe, or NH_2), while reaction in acetic acid would lead to the isomeric aminotetra-azaindenes (XX). However, both types of reaction gave the same products; each contained a cyano-group but analyses excluded the crotonate structures (XIX), and the cyanotetra-azaindene formulations (XXI) are postulated. Compounds (XXI; R = SMe or NH_2) were obtained directly: compound (XXI; R = H) was obtained as its 3-aminotriazole salt, whence acid liberated the free oxo-compound.

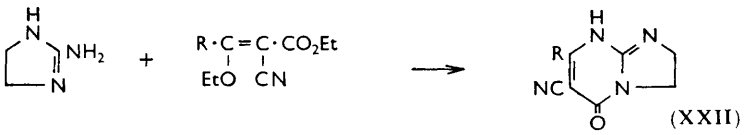

(XIX)


(XX)


(XXI)

The reaction of the acrylate (VII; R = H) with 2-aminoimidazoline carbonate has also been investigated. Unlike the reaction with 3-aminotriazole, fusion gave 5-cyano-1,2,4,7-tetrahydro-4-oxo-1,3a,7-triazaindene (XXII; R = H) (cf. XVIII), and not one of the

esters. Similarly the cyanocrotonate (VII; R = Me) and aminoimidazoline carbonate give the cyanotriazaindene (XXII; R = Me).



(XXII)

Experimental

Infrared measurements were made on potassium bromide discs; analyses are by Mr. C. B. Dennis.

Ethyl α-(1,2,4-*Triazol*-3-*ylamino*)*methylenemalonate* (V).—This *compound* was prepared by Heimbach and Kelly's method [4] in 11·5% yield, forming needles, m. p. 180—181° (Found: C, 47·3; H, 5·5; N, 21·7. $C_{10}H_{14}N_4O_4$ requires C, 47·3; H, 5·5; N, 22·0%).

Ethyl α-(*Ethoxy*-5-*methylthio*-1,2,4-*triazol*-3-*ylamino*)*methylmalonate* (VI).—This *compound* was prepared as above but from 3-amino-5-methylthio-1,2,4-triazole (13·0 g.). When recrystallized from aqueous alcohol, it had m. p. 108—109° (11·5 g.) (Found: C, 44·7; H, 6·7; N, 16·0; S, 9·4. $C_{13}H_{22}N_4O_5S$ requires C, 45·0; H, 6·4; N, 16·2; S, 9·2%).

Action of Acetic Acid on Compound (V).—Compound (V) (1 g.) was refluxed for 2½ hr. in acetic acid (10 c.c.). On chilling, the ester (I; R = R′ = H) separated and recrystallized from water to give a product (0·4 g.), m. p. 252—254°, identical with that previously described.[3]

Action of Acetic Acid on Compound (VI).—The above procedure was repeated with compound (VI) (1 g.). The product (I; R = SMe, R′ = H) (0·2 g.), recrystallized from acetic acid, had m. p. 309—310° and was identical with that obtained by the method of Allen *et al.*[3]

Ethyl 6,7-*Dihydro*-2-*methylthio*-6-*oxo*-1,3,3a,7-*tetra-azaindene*-5-*carboxylate* (II; R = SMe, R′ = H).—Sodium (2·3 g.) was dissolved in alcohol (60 c.c.), to this solution 3-amino-5-methylthio-1,2,4-triazole (13 g.) and ethyl β-ethoxy-α-ethoxycarbonylacrylate (21·6 g.) were added, and the mixture was refluxed overnight. Water (400 c.c.) was then added and the whole boiled. While still hot the solution was acidified with hydrochloric acid and then cooled. The resulting crystals were the ester (I; R = SMe, R′ = H), m. p. 309—310°. The filtrate was chilled for several hours, whereupon colourless crystals separated. These recrystallized from water to give the *product* (II; R = SMe, R′ = H) (2 g.), m. p. 209—210° (Found: C, 42·7; H, 4·2; N, 21·8; S, 12·9. $C_9H_{10}N_4O_3S$ requires C, 42·6; H, 4·0; N, 22·0; S, 12·6%).

Ethyl α-*Cyano*-β-(1,2,4-*triazol*-3-*ylamino*)*acrylate* (XIII; R = H).—Ethyl α-cyano-β-ethoxyacrylate (8·4 g.) and 3-amino-1,2,4-triazole (4·2 g.) were heated together in an oil-bath. At 125—128° a reaction occurred and alcohol was evolved. The melt solidified and heating was discontinued. The *product*, when recrystallized from 70% aqueous acetic acid, had m. p. 202—204° (10 g.) (Found: C, 46·4; H, 4·9; N, 33·7. $C_8H_9N_5O_2$ requires C, 46·4; H, 4·4; N, 33·8%).

Ethyl α-*Cyano*-β-(5-*methylthio*-1,2,4-*triazol*-3-*ylamino*)*acrylate* (XIII; R = SMe).—Ethyl α-cyano-β-ethoxyacrylate (4·2 g.) and 3-amino-5-methylthio-1,2,4-triazole (3·25 g.) were heated together as in the above reaction. The *product*, recrystallized from 50% aqueous acetic acid, had m. p. 184—186° (1·0 g.) (Found: C, 43·0; H, 4·5; N, 28·4; S, 12·9. $C_9H_{11}N_5O_2S$ requires C, 42·7; H, 4·4; N, 27·7; S, 12·7%).

Ethyl 4-*Amino*-1,3,3a,7-*tetra-azaindene*-5-*carboxylate* (XIV; R = H).—(*a*) Ethyl α-cyano-β-ethoxyacrylate (4·2 g.) and 3-amino-1,2,4-triazole (2·1 g.) were refluxed together in acetic acid (50 c.c.) for 3 hr. After chilling, the solid *product* was collected and recrystallized from water containing a few drops of acetic acid, giving needles (1·8 g.), m. p. 224—225° (Found: C, 46·7; H, 4·7; N, 33·7. $C_8H_9N_5O_2$ requires C, 46·4; H, 4·4; N, 33·9%).

(*b*) Ethyl α-cyano-β-(1,2,4-triazol-3-ylamino)acrylate was heated under reflux in acetic acid (10 c.c./g.) for 45 min. After chilling, the product was collected and recrystallized as in (*a*); it had m. p. 224—225° alone or mixed with a sample made according to (*a*) (Found: C, 47·2; H, 4·8; N, 34·1%).

Ethyl 4-*Amino*-2-*methylthio*-1,3,3a,7-*tetra-azaindene*-5-*carboxylate* (XIV; R = SMe)—(*a*) Ethyl α-cyano-β-ethoxyacrylate (4·2 g.) and 3-amino-5-methylthio-1,2,4-triazole (3·25 g.) were refluxed together in acetic acid (30 c.c.) for 3 hr. After cooling, ether (30 c.c.) was added and the *product* collected and recrystallized from aqueous acetic acid; it (3·9 g.) had m. p. 214—

216° (Found: C, 42·8; H, 4·6; N, 27·8; S, 12·6. $C_9H_{11}N_5O_2S$ requires C, 42·7; H, 4·4; N, 27·7; S, 12·7%).

(*b*) Ethyl α-cyano-β-(5-methylthio-1,2,4-triazol-3-ylamino)acrylate (0·5 g.) was refluxed in acetic acid (5 c.c.) for 45 min. After chilling, the product was collected and recrystallized as above to give a solid (0·25 g.), m. p. and mixed m. p. 214—216° (Found: C, 42·7; H, 4·9; N, 27·5; S, 12·9%).

5-*Cyano*-4,7-*dihydro*-4-*oxo*-1,3,3a,7-*tetra-azaindene* (XVIII; R = H).—Sodium (2·3 g.) was dissolved in ethanol (60 c.c.), 3-amino-1,2,4-triazole (8·4 g.) was added, then ethyl α-cyano-β-ethoxyacrylate (16·9 g.), and the mixture brought rapidly to the boil. A clear solution resulted, but almost immediately a precipitate was formed and the whole solidified. Water (100 c.c.) was added and the mixture was warmed on the steam-bath until dissolution was complete. It was then acidified and chilled, to give a mixture which was recrystallized from water. The crystallized mixture was suspended in cold water, and sodium carbonate added slowly until no more carbon dioxide was evolved. The insoluble amino-ester (XIV; R = H) was removed and recrystallized from water, to give 2 g. of material. The filtrate was acidified with hydrochloric acid, and the precipitate collected and recrystallized from water, to give the *product* (XVIII; R = H) (3·5 g.), m. p. 305—307° (Found: C, 44·9; H, 2·6; N, 43·9. $C_6H_3N_5O$ requires C, 44·9; H, 1·9; N, 43·5%).

5-*Cyano*-4,7-*dihydro*-2-*methylthio*-4-*oxo*-1,3,3a,7-*tetra-azaindene* (XVIII; R = SMe).—3-Amino-5-methylthio-1,2,4-triazole (6·5 g.) was added to a solution from sodium (1·15 g.) in ethanol (60 c.c.). To this ethyl α-cyano-β-ethoxyacrylate (8·45 g.) was added and the solution refluxed for 1½ hr., by which time a considerable amount of solid had separated. Water (60 c.c.) was added to dissolve the solid, and the solution acidified with hydrochloric acid. The precipitate was collected and recrystallized from 50% acetic acid, giving 4 g. of a mixture. Sodium carbonate (8 g.), in water (60 c.c.), was added to the above mixture (4 g.), and the suspension was warmed (50—60°) on the steam-bath. The undissolved solid was collected and recrystallized from 50% acetic acid, to give the ester (XIV; R = SMe), m. p. 214—216° (2·1 g.). The filtrate was cooled, again filtered, and acidified with hydrochloric acid. The solid *product* (XVIII; R = SMe) was collected and recrystallized from 50% acetic acid (yield, 1·7 g.); it had m. p. 318—320° (Found: C, 40·9; H, 2·9; N, 34·2; S, 15·7. $C_7H_5N_5OS$ requires C, 40·6; H, 2·4; N, 33·9; S, 15·5%).

4-*Amino*-1,3,3a,7-*tetra-azaindene*-5-*carboxylic Acid* (XVII).—(*a*) Ethyl α-cyano-β-(1,2,4-triazol-3-ylamino)acrylate (2·5 g.) was warmed in 12% sodium hydroxide solution (25 c.c.) on the steam-bath for 3 min. The solution was chilled and acidified with dilute hydrochloric acid, to give a colourless precipitate which recrystallized from 75% acetic acid, affording the *acid* (XVII) (0·40 g.), m. p. 292—293° (Found: C, 40·0; H, 3·2; N, 39·8. $C_6H_5N_5O_2$ requires C, 40·2; H, 2·8; N, 39·1%).

(*b*) By the above reaction the ester (XIII; R = H) gave crystals, m. p. 292—293° (Found: C, 40·5; H, 3·3; N, 38·8%).

Action of Sodium Ethoxide on the Ester (XIII; R = H).—Ethyl α-cyano-β-(1,2,4-triazol-3-ylamino)acrylate (2·9 g.) was refluxed for 2 hr. in alcohol (20 c.c.) in which sodium (0·32 g.) had been dissolved. Water (20 c.c.) was added; the solid dissolved, and the solution was cooled to room temperature and left for 1½—2 hr. The precipitate was removed and after recrystallization from aqueous acetic acid gave ester (XIV; R = H) (1·3 g.), m. p. 224—225°. The filtrate was acidified and evaporated to dryness under a vacuum, and the residue recrystallized from water to give the cyanoazaindene (XVIII; R = H) (0·3 g.), m. p. 306—307°.

5-*Cyano*-4,7-*dihydro*-6-*methyl*-4-*oxo*-1,3,3a,7-*tetra-azaindene* (XXI; R = H).—Ethyl α-cyano-β-ethoxycrotonate (18·3 g.) and 3-amino-1,2,4-triazole (8·4 g.) were refluxed together in acetic acid (60 c.c.) for 6 hr. On chilling, a solid separated which recrystallized from water to give the *aminotriazole salt* (10 g.), m. p. 275—277°, of the product (Found: C, 39·4; H, 4·0; N, 45·7. $C_9H_9N_9O,H_2O$ requires C, 39·2; H, 4·0; N, 45·7%). The *tetra-azaindene*, m. p. 301—302°, was obtained by the acidification of an aqueous solution of this salt (Found: C, 48·2; H, 3·0; N, 40·2. $C_7H_5N_5O$ requires C, 48·0; H, 2·9; N, 40·2%).

5-*Cyano*-4,7-*dihydro*-6-*methyl*-2-*methylthio*-4-*oxo*-1,3,3a,7-*tetra-azaindene* (XXI; R = SMe).—3-Amino-5-methylthio-1,2,4-triazole (13·0 g.) and ethyl α-cyano-β-ethoxycrotonate (18·3 g.) condensed as in the previous preparation. In this reaction the product was isolated directly and recrystallized from water to give the *product* (4·5 g.), m. p. 300° (decomp.) (Found: C, 43·6; H, 3·7; N, 31·1; S, 14·4. $C_8H_7N_5OS$ requires C, 43·5; H, 3·2; N, 31·6; S, 14·4%).

5-*Cyano*-1,2,4,7-*tetrahydro*-4-*oxo*-1,3a,7-*triazaindene* (XXII; R = H).—Ethyl α-cyano-β-ethoxyacrylate (8 g.) and 2-aminoimidazoline carbonate [11] (4 g.) were heated together at 130° (bath). Alcohol was evolved, and the melt solidified. After cooling, it recrystallized from water, to give the *product* (2·0 g.), m. p. 297° (Found: C, 51·9; H, 4·4; 34·3. $C_7H_6N_4O$ requires C, 51·9; H, 3·7; N, 34·6%).

5-*Cyano*-1,2,4,7-*tetrahydro*-6-*methyl*-4-*oxo*-1,3a,7-*triazaindene* (XXII; R = Me).—This *product* was obtained similarly from ethyl α-cyano-β-ethoxycrotonate (4·3 g.) and 2-aminoimidazoline carbonate (2 g.). Recrystallized from aqueous alcohol, it (1·5 g.) had m. p. 336° (Found: C, 54·5; H, 4·9; N, 31·9. $C_8H_8N_4O$ requires C, 54·6; H, 4·5; N, 31·9%).

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[11] Stefayne and Howard, *J. Amer. Chem. Soc.*, 1955, **77**, 761.