Action of Isoxazol-5-ones on Schiff's Bases

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3-Phenylisoxazol-5-one reacts with Schiff's bases to give substituted ammonium 4-[α-(5-hydroxy-3-phenylisoxazol-4-yl)benzyl]3-phenylisoxazol-5-olates, the cations being derived from the basic components of the Schiff's bases. Analogous salts are obtained from the action of amines on 4-arylmethylene-3-phenylisoxazol-5-ones.

AROMATIC aldehydes condense readily with isoxazol-5-ones unsubstituted in the 4-position to produce 4-arylmethyleneisoxazol-5-ones.[1-3] Schiff's bases, which are similar in many respects to the aldehydes from which they are derived, also condense with compounds containing active methylene groups. Thus *N*-benzylideneaniline condenses with 2-phenyloxazol-5(4*H*)-one to give a mixture of α-benzamidocinnamanilide and 4-benzylidene-2-phenyloxazol-5-one.[4]

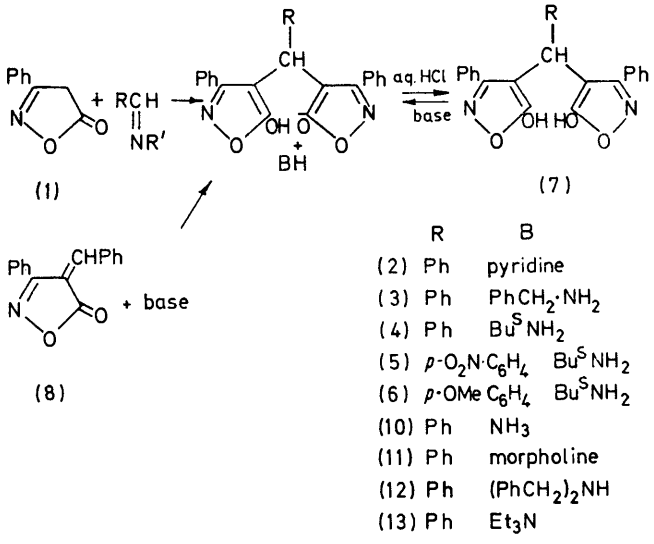
We have previously [5] reported the action of isoxazol-5-ones on enamines to give ammonium 4-alkenylisoxazol-5-olates. We have now studied the action of isoxazol-5-ones on Schiff's bases, with unexpected results.

Reaction of 3-phenylisoxazol-5-one (1) with Schiff's bases derived from aromatic aldehydes, in pyridine at room temperature, gave compounds characterised as the amine salts (2)—(6). In the case of *N*-benzylideneaniline, aniline (pK_a 4·58) [6] is displaced by the solvent pyridine (pK_a 5·23) [6] and the pyridinium salt (2) is obtained. The salts (2)—(6) were identified from chemical and spectroscopic data.

Treatment of these salts with aqueous hydrochloric acid gave the corresponding free acids, the 4,4'-benzylidenebis-(3-phenylisoxazol-5-ol)s (7) which were readily reconverted into the salts by base. The

[1] A. Meyer, *Compt. rend.*, 1912, **155**, 841; *Ann. chim. Phys.*, 1914, **1**, 252.
[2] A. Wahl and C. Silbergweig, *Bull. Soc. chim. France*, 1913, **13**, 236.
[3] A. Wahl and J. Rolland, *Ann. chim. (France)*, 1928, **10**, 5.
[4] A. B. A. Jansen and R. Robinson, *Monatsh.*, 1967, **98**, 1020.
[5] A. M. Knowles and A. Lawson, *J.C.S. Perkin I*, 1972, 1240.
[6] A. Albert and E. P. Serjeant, in 'Ionisation Constants of Acids and Bases,' Methuen, London, 1962, p. 144.

analogous salt, s-butylammonium 4-[α-(5-hydroxy-3-methylisoxazol-4-yl)benzyl]-3-methylisoxazol-5-olate, prepared by the action of s-butylamine on 4-benzylidene-3-methylisoxazol-5-one gave the known acid 4,4'-benzylidenebis-(3-methylisoxazol-5-ol), which has been



	R	B
(2)	Ph	pyridine
(3)	Ph	$PhCH_2 \cdot NH_2$
(4)	Ph	$Bu^S NH_2$
(5)	p-$O_2N \cdot C_6H_4$	$Bu^S NH_2$
(6)	p-$OMe\ C_6H_4$	$Bu^S NH_2$
(10)	Ph	NH_3
(11)	Ph	morpholine
(12)	Ph	$(PhCH_2)_2NH$
(13)	Ph	Et_3N

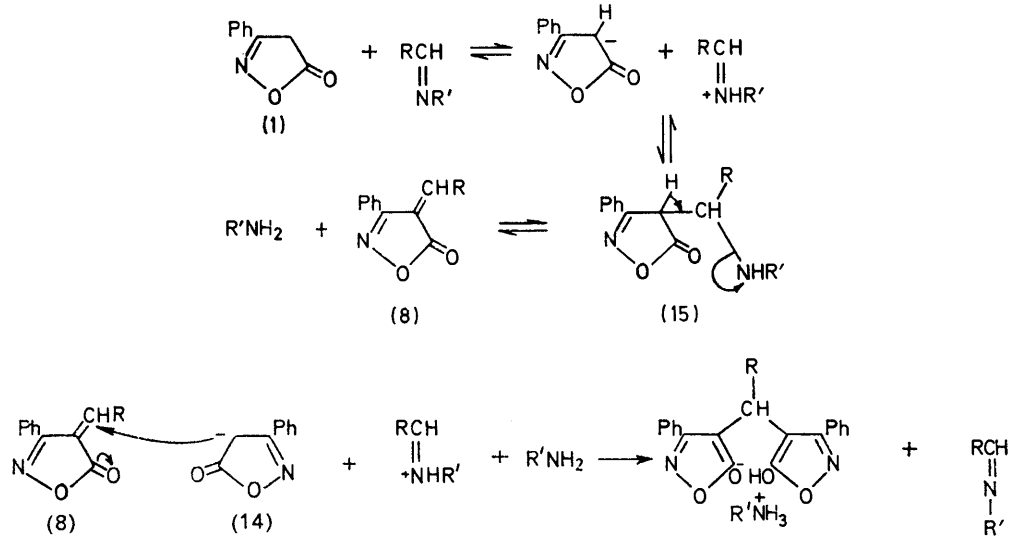
obtained from the reaction of 4-benzylidene-3-methylisoxazol-5-one with alkali.[7,8] Attempts to produce the 3-phenyl analogue by the same method were however unsuccessful.[7]

The i.r. spectra of the salts (2)—(6) show absorption at 3070 cm^{-1} suggestive of an intramolecularly hydrogen-bonded hydroxyl-group,[9] and a broad NH^+ peak in the region 2900—2400 cm^{-1}.[10] Strong absorption at 1635 cm^{-1} is assigned to the carbonyl group and C=N absorption appears at 1615 cm^{-1}.[11] The large shift to lower frequency of the carbonyl absorption in the salts compared with the parent isoxazolone ($\nu_{max.}$ 1800 cm^{-1}) has been observed with the 4-alkenylisoxazol-5-olates[5] derived from enamines.

The n.m.r. spectra of the salts (2)—(6) show a singlet at τ 5·23 due to the benzylic proton and the NH signals appear, as expected, in the region τ 1—2. The absorption due to OH is not observed. The n.m.r. spectrum of the free acids show a singlet at τ 5·0 (1H) due to the benzylic proton and a broad peak in the region −1·2 to −1·6 (2H) due to OH; this was not observed in the spectrum of the diacetyl derivative.

With 4-benzylidene-3-phenylisoxazol-5-one (8) and ammonia or a primary or secondary amine, the corresponding amine salts (10)—(12) are obtained. The tertiary amine salts (2) and (13) could not be formed by direct reaction of the amine with compound (8) but only in the presence of a primary amine of lower pK_a value.

The mechanism of formation of these salts from 3-phenylisoxazol-5-one and Schiff's bases is apparently complex and appears to involve the intermediate formation of 4-benzylidene-3-phenylisoxazol-5-one (8). This undergoes nucleophilic attack at the methine carbon atom by the anion (14) of the 3-phenylisoxazol-5-one in the presence of the primary amine formed as a result of the breakdown of the addition product (15) (Scheme 1)



SCHEME 1

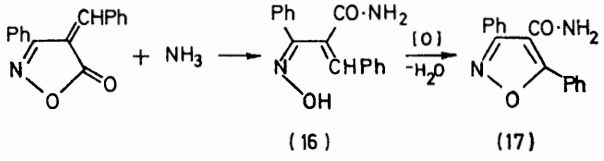
Supporting evidence for this is the formation of these salts by the reaction of pre-formed 4-benzylidene-3-phenylisoxazol-5-one (8) with a primary or secondary amine, which can be visualised as involving the partial decomposition of (8) *via* (15) to the anion (14) of the isoxazolone. Further evidence suggesting the role of the 3-phenylisoxazolone anion in the mechanism was

[7] A. J. Donleavy and E. E. Gilbert, *J. Amer. Chem. Soc.*, 1937, **59**, 1072.
[8] A. Ehsan, S. Ali, I. Ahmed, and Karimullah, *Pak. J. Sci. Ind. Res.*, 1967, **10**, 228.
[9] L. J. Bellamy, in 'The Infra-red Spectra of Complex Molecules,' Methuen, London, 1964, p. 104.
[10] Ref. 9, p. 260.
[11] A. J. Boulton and A. R. Katritzky, *Tetrahedron*, 1961, **12**, 41.

obtained in the isolation of the pyridinium salt (2) from the reaction of 3-phenylisoxazol-5-one (1) with its 4-benzylidene derivative (8) in the presence of pyridine as solvent. Pyridine, unlike primary and secondary amines, does not react with 4-benzylidene-3-phenylisoxazol-5-one alone, presumably because of the impossibility under these conditions of providing a route to the anion.

Betti [12] has described the reaction in ethanol of 4-benzylidene-3-phenylisoxazol-5-one with ammonia in the presence of a small amount of benzaldehyde. After several days at room temperature 3,5-diphenylisoxazole-4-carboxamide (17) was produced. We have confirmed this result. However, if after a few hours at room temperature the reaction mixture is worked up, the ammonium salt (10) is the only isolable product.

To account for his result Betti suggested a mechanism involving nucleophilic attack by ammonia at the 5-carbonyl carbon atom of the isoxazolone ring to form the amide (16), which subsequently underwent oxidation by atmospheric oxygen in the presence of benzaldehyde to produce the isoxazole (17) (Scheme 2).



(16) (17)

SCHEME 2

The conversion of the amide (16) into the isoxazole (17) by spontaneous oxidation in the presence of benzaldehyde seems unusual. In view of our findings, the mechanism probably involves the initial formation of the ammonium salt (10), which then undergoes decomposition to the isoxazole amide (17). Evidence of this was obtained in the isolation of the isoxazole (17) in high yield from a mixture of the salt (10), benzaldehyde, and ammonia left at room temperature for several days.

EXPERIMENTAL

I.r. spectra were determined for KBr discs; n.m.r. spectra were measured at 60 MHz. All solvents were dried, pyridine and ethanol over molecular sieve pellets (Grade 3A) and ether over sodium.

s-Butylammonium 4-[α-(5-*Hydroxy*-3-*phenylisoxazol*-4-*yl*)-*benzyl*]-3-*phenylisoxazol*-5-*olate* (4).—(*a*) A solution of 3-phenylisoxazol-5-one [13] (4·6 g) in anhydrous pyridine (50 ml) was stirred at room temp. with *N*-benzylidene-s-butylamine [14] (4·6 g). After 15 h the solvent was removed and the resulting oil triturated with ethanol–ether. The *product* (7·0 g, 51%), had m.p. 206—208° (from ethanol), $\nu_{max.}$ 3070, 2950—2550br, 1635 and 1615 cm^{-1}, τ [$(CD_3)_2SO$] 1·8—2·4 (3H, s, $^+NH_3$), 2·4—3·0 (15H, m, 3 × Ph), 5·23 (1H, s, PhC*H*), and 8·2—9·4 (9H, m, Bu^s) (Found: C, 72·1; H, 6·3; N, 8·7. $C_{29}H_{29}N_3O_4$ requires C, 72·1; H, 6·0; N, 8·7%).

(*b*) A solution of 4-benzylidene-3-phenylisoxazol-5-one (2·0 g) [1-3] in pyridine (30 ml) was treated with s-butylamine (1·2 g). After 15 h at room temp the solvent was removed and the resulting oil triturated with ethanol–ether to give the salt (4) (1·4 g, 36%).

(*c*) A solution of 4,4′-benzylidenebis-(3-phenylisoxazol-5-ol) (1·5 g) in pyridine (20 ml) was treated with s-butylamine (2·0 ml) at room temp. The solvent was removed after 1 h and the resulting oil triturated with ethanol–ether, to give the salt (4) (1·0 g, 56%).

(*d*) A solution of 3-phenylisoxazol-5-one (1·6 g) and 4-benzylidene-3-phenylisoxazol-5-one (2·5 g) in pyridine (30 ml) was treated with s-butylamine (2·0 ml) at room temp. After 15 h the solvent was removed and the resulting oil triturated with ethanol–ether to give the salt (4) (4·0 g, 83%).

Pyridinium 4-[α-(5-*Hydroxy*-3-*phenylisoxazol*-4-*yl*)*benzyl*]-3-*phenylisoxazol*-5-*olate* (2).—(*a*) A solution of 3-phenylisoxazol-5-one [13] (7·0 g) in pyridine (50 ml) was stirred with *N*-benzylideneaniline [14] (8·0 g) at room temp. After 15 h the solvent was removed and the resulting oil triturated with ethanol–ether. Recrystallisation from ethanol gave the *pyridinium salt* (11·0 g, 51%), m.p. 150—153°), $\nu_{max.}$ 3070, 2900—2500br, 1635, and 1615 cm^{-1}, τ [$(CD_3)_2SO$] 1·0—2·3 (6H, m, pyridinium [15]), 2·5—2·9 (15H, m, 3 × Ph), and 5·23 (1H, s, PhC*H*) (Found: C, 73·6; H, 5·4; N, 8·3. $C_{30}H_{25}N_3O_4$ requires C, 73·3; H, 5·1; N, 8·6%).

(*b*) When 3-phenylisoxazol-5-one [13] (1·61 g) in pyridine (50 ml) was treated with 4-benzylidene-3-phenylisoxazol-5-one [1-3] (2·5 g) at room temp. the pyridinium salt (2) (4·5 g, 90%) was obtained.

(*c*) 4,4′-Benzylidenebis-(3-phenylisoxazol-5-ol) (7; R = Ph) (1·0 g) was dissolved in pyridine (10 ml). After 2 min the solvent was removed and the resulting oil triturated with ethanol–ether to give the pyridinium salt (2) (1·2 g, 100%).

(*d*) A suspension of 4-benzylidene-3-phenylisoxazol-5-one (5·0 g) in pyridine (50 ml) was treated with aniline (2·9 g) at room temp. After 15 h the solvent was removed and the resulting oil triturated with ethanol–ether to give the pyridinium salt (2) (5·0 g, 33%).

In a similar manner to the salt (4) were obtained the *benzylammonium salt* (3) (5·0 g, 62%) from 3-phenylisoxazol-5-one (2·5 g) and *N*-benzylidenebenzylamine [14] (3·1 g), m.p. 183—185°, $\nu_{max.}$ 3070, 2800—2650br, 1635, and 1615 cm^{-1} (Found: C, 74·0; H, 5·2; N, 8·3. $C_{32}H_{27}N_3O_4$ requires C, 74·3; H, 5·2; N, 8·1%); *s-butylammonium* 4-[α-(5-*hydroxy*-3-*phenylisoxazol*-4-*yl*)-p-*nitrobenzyl*]-3-*phenylisoxazol*-5-*olate* (5) (10·0 g, 38%) from 3-phenylisoxazol-5-one and *N*-p-nitrobenzylidene-s-butylamine [14] (10·3 g), m.p. 166—168°, $\nu_{max.}$ 3070, 2980—2600br, 1635, and 1615 cm^{-1}, τ [$(CD_3)_2SO$] 2·2—2·4 (3H, s, $^+NH_3$), 2·5—3·0 (14H, m, aromatic), 5·25 (1H, s, C_6H_4·C*H*), and 8·2—9·4 (9H, m, Bu^s) (Found: C, 65·5; H, 5·6; N, 10·1. $C_{29}H_{28}N_4O_6$ requires C, 65·9; H, 5·3; N, 10·6%); and the p-*methoxy-analogue* (6) (5·0 g, 47%) from 3-phenylisoxazol-5-one (3·2 g) and *N*-p-methoxybenzylidene-s-butylamine [14] (3·8 g), m.p. 179—181°, $\nu_{max.}$ 3020, 2950—2550br, 1635, and 1615 cm^{-1}, τ [$(CD_3)_2SO$] 2·2—2·4 (3H, s. $^+NH_3$), 2·5—3·3 (14H, m, aromatic), 5·45 (1H, s, C_6H_4·C*H*), and 8·3—9·4 (9H, m, Bu^s) (Found: C, 70·1; H, 6·1; N, 8·2. $C_{30}H_{31}N_3O_5$ requires C, 70·2; H, 6·0; N, 8·2%). In this

[12] M. Betti, *Gazzetta*, 1915, 45(i), 362.
[13] A. Hantzsch, *Ber.*, 1891, **24**, 495.
[14] R. B. Moffett and W. M. Hoehn, *J. Amer. Chem. Soc.*, 1947, **69**, 1792.
[15] High Resolution NMR Spectra Catalog, Vol. 1, Varian Associates, 1962, Spectrum no. 96.

last reaction 4-*p*-methoxybenzylidene-3-phenylisoxazol-5-one (1·2 g, 21%), m.p. 165—166° (lit.,[8] 164—165°), $\nu_{max.}$ 1734 and 1623 cm^{-1}, was also isolated.

The *dibenzylammonium Salt* (12).—A solution of 4-benzylidene-3-phenylisoxazol-5-one (1·3 g) in pyridine (50 ml) was treated with dibenzylamine (1·97 g). After 15 h the solvent was removed and the resulting oil triturated with ethanol–ether. The *product* (12) (1·5 g, 47%) had m.p. 184—186° (from ethanol), $\nu_{max.}$ 3040, 2800—2450br, 1635, and 1615 cm^{-1}, τ [$(CD_3)_2SO$] 1·0—2·3 (2H, $^+NH_2$), 2·4—3·2 (25H, m, 5 × Ph), 5·23 (1H, s, PhC*H*), and 5·85 (4H, s, 2 × CH_2) (Found: C, 76·6; H, 5·5; N, 6·8. $C_{39}H_{34}N_3O_4$ requires C, 76·9; H, 5·6; N, 6·9%). Likewise, the *morpholinium salt* (11) (1·5 g, 58%) was obtained from 4-benzylidene-3-phenylisoxazol-5-one (1·3 g) and morpholine (0·9 g, 2 equiv.), m.p. 206—207°, $\nu_{max.}$ 2980, 2850, 2770, 2650, 2480, 1635, and 1615 cm^{-1} (Found: C, 69·7; H, 5·7; N, 8·7. $C_{29}H_{27}N_3O_5$ requires C, 70·0; H, 5·4; N, 8·5%).

The Ammonium Salt (10).—(*a*) A solution of 4-benzylidene-3-phenylisoxazol-5-one in ethanol (30 ml) was treated with ammonia (*d* 0·880; 2·0 ml) and warmed for a few minutes on a steam-bath. After 1 h at room temp. the solvent was removed; the *product* (10) (1·0 g, 58%) had m.p. 189—190° (from ethanol), $\nu_{max.}$ 3200, 3070, 3000—2750br, 1635, and 1615 cm^{-1}, τ [$(CD_3)_2SO$] 2·6—3·2 (19H, m, aromatic and $^+NH_4$) (15H after treatment with D_2O) and 5·4 (1H, s, PhC*H*) (Found: C, 70·0; H, 5·1; N, 9·7. $C_{25}H_{23}N_3O_4$ requires C, 70·0; H, 5·4; N, 9·8%).

(*b*) A solution of 4-benzylidene-3-phenylisoxazol-5-one in ethanol (25 ml) saturated with anhydrous ammonia also gave the salt (10) (2·0 g, 80%).

The Triethylammonium Salt (13).—(*a*) A solution of 4-benzylidene-3-phenylisoxazol-5-one in ethanol (50 ml) was treated with triethylamine (1·0 g) and aniline (0·93 g). After 15 h at room temp. the solvent was removed and the resulting oil triturated with ethanol–ether. The *product* (13) (2·5 g, 49%) had m.p. 119—121° (from ethanol), $\nu_{max.}$ 3000, 2680, 2520, 1635, and 1615 cm^{-1}, τ ($CDCl_3$) 2·6—3·0 (16H, s, aromatic and ^+NH), 5·23 (1H, s, PhC*H*), 7·0—7·4 (6H, q, 3 × CH_2Me), and 8·8—9·2 (9H, t, 3 × $CH_3{\cdot}CH_2$) (Found: C, 72·7; H, 6·9; N, 8·7. $C_{31}H_{33}N_3O_4$ requires C, 72·8; H, 6·5; N, 8·2%).

(*b*) The product (13) (2·0 g, 80%) was also obtained from 4,4′-benzylidenebis-(3-phenylisoxazol-5-ol) (7) (2·0 g) and triethylamine (1·01 g, 2 equiv.) in ethanol (30 ml) at room temp.

(*c*) Treatment of the pyridinium salt (2) (1·8 g) with triethylamine (1·01 g, 2 equiv.) also gave the salt (13) (1·4 g, 57%).

s-Butylammonium 4-[α-(*5-Hydroxy-3-methylisoxazol-4-yl*)-*benzyl*]-3-*methylisoxazol-5-olate*.—A suspension of 4-benzylidene-3-methylisoxazol-5-one [8] (1·9 g) in ethanol (30 ml) was treated with s-butylamine at room temp. After 15 h the solvent was removed and the resulting oil triturated with ether. The *product* (1·0 g, 28%) had m.p. 165—167° (from ethanol), $\nu_{max.}$ 3070, 2950—2450, 1635, and 1600 cm^{-1} (Found: C, 63·7; H, 7·0; N, 11·5. $C_{19}H_{25}N_3O_4$ requires C, 63·5; H, 7·0; N, 11·7%).

4,4′-*Benzylidenebis-*(3-*phenylisoxazol-5-ol*) (7).—(*a*) A solution of the pyridinium salt (2) (3·0 g) in ethanol (100 ml) was saturated with hydrogen chloride at room temp. The solvent was removed and the resulting oil was triturated with ethanol–ether. The *product* (1·1 g, 33%) had m.p. 156—160° (from ethanol), $\nu_{max.}$ 3050, 2800, 1665, and 1615 cm^{-1}, τ [$(CD_3)_2SO$] −1·6 to −1·3 (2H, s, 2 × OH), 2·6—3·0 (15H, m, 3 × Ph), and 4·98 (1H, s, PhC*H*) (Found: C, 73·2; H, 4·6; N, 7·0. $C_{25}H_{18}N_2O_4$ requires C, 73·2; H, 4·4; N, 6·8%).

(*b*) A solution of the pyridinium salt (2) (5·0 g) in ethanol (20 ml) when treated with aqueous hydrochloric acid (3N; 5 ml) gave the acid (7) (4·0 g, 96%).

4,4′-*Benzylidenebis-*(3-*methylisoxazol-5-ol*).—A solution of the corresponding s-butylammonium salt (1·0 g) in ethanol (20 ml) when treated with aqueous hydrochloric acid (3N; 2·0 ml) gave the product (0·6 g, 74%), m.p. 153—155° (from ethanol) (lit.,[8] 150—152°) (Found: C, 63·0; H, 4·8; N, 9·9. Calc. for $C_{15}H_{14}N_2O_4$: C, 62·9; H, 4·9; N, 9·8%).

4,4′-*Benzylidenebis-*(3-*phenylisoxazol-4-yl*) *Diacetate* (9).—A solution of the free acid (7) (2·0 g) in pyridine (20 ml) was treated with acetic anhydride (5·0 ml). After 1 h at room temp. the solution was poured on ice containing concentrated hydrochloric acid (20 ml). The oil solidified in a few minutes. The *product* had m.p. 147—148° (from ethanol), $\nu_{max.}$ 1760, 1720, 1625, and 1610 cm^{-1}, τ ($CDCl_3$) 2·5—3·0 (15H, m, 3 × Ph), 5·3 (1H, s, PhC*H*), and 7·7 (6H, s, 2 × Me) (Found: C, 70·8; H, 5·0; N, 5·6. $C_{29}H_{22}N_2O_6$ requires C, 70·5; H, 4·5; N, 5·7%).

3,5-*Diphenylisoxazole-*4-*carboxamide* (17).—(*a*) 4-Benzylidene-3-phenylisoxazol-5-one (2·5 g) was dissolved in ethanol (25 ml) saturated with anhydrous ammonia and treated with benzaldehyde (1·0 ml). After 1 h on the steam-bath ammoniacal ethanol (20 ml) was added to the cool solution. After 3 days at room temp. the product was isolated (2·0 g, 76%); m.p. 236—238° (lit.,[12] 229—230°), $\nu_{max.}$ 3320, 3130, 1660, 1643, and 1600 cm^{-1} (Found: C, 72·2; H, 4·6; N, 10·8. Calc. for $C_{16}H_{12}N_2O_2$: C, 72·2; H, 4·55; N, 10·6%).

(*b*) A solution of the ammonium salt (10) (1·5 g) in ethanol (25 ml) was treated with ammonia (*d* 0·880; 3·0 ml), and benzaldehyde (1·0 ml) at room temp. After 10 days the solvent was removed and the residual oil when triturated with ethanol–ether gave the amide (17) (0·5 g, 54%).

[2/2386 *Received*, 18*th October*, 1972]