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ISATOGENS V. A NEW SYNTHESIS OF Δ^4-ISOXAZOLINES.

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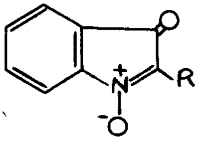
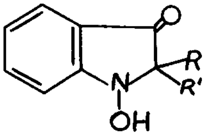
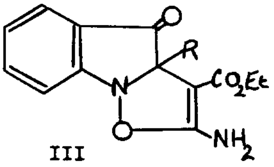
Recent interest in isatogens (1-7) and isoxazolines (8-13) prompts us to report our own work in this field. We are at present engaged in a systematic study of the reactivity of isatogens towards nucleophilic reagents.



I



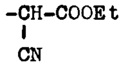
II



III

R.

a, $-COOCH_3$
b, 2-pyridyl
c, p-nitrophenyl
d, phenyl

R' = $C_5H_{10}N-$
$-OEt$ or

$-\underset{\text{CN}}{\underset{|}{\text{CH}}}-\text{COOEt}$

Although previous workers have described the formation of N-hydroxyindolin-3-ones (II) from the reaction of nucleophiles (14-16) with isatogens we formulate the products obtained by the reaction of the isatogens (I, a-d) with ethyl cyanacetate (16), from spectroscopic data, as the previously unknown Δ^4-isoxazolines (III, a-d). The reaction took place readily on stirring the reactants in cold ethanol, with piperidine as catalyst, the products separating from the reaction mixtures as white solids which crystallised from ethanol in white needles (table 1).

TABLE 1.

	Time	Yield	m.p.
IIIa	12 hrs.	90%	198-200°(decomp.)
IIIb	24 hrs.	60%	166°(decomp.)
IIIc	60 hrs.	55%	165-166°(decomp.)
IIId	60 hrs.	95%	158-160°(decomp.)

All elemental analyses were satisfactory. 2-p-Methoxyphenylisatogen (I; R = p-methoxyphenyl) also reacted with ethyl cyanacetate under these conditions but the product was not readily isolable.

The infrared spectra of these compounds showed two bands of medium intensity at 3,300 and 3,225 cm.$^{-1}$ in the solid which became slightly sharper and moved to 3,450 and 3,350 cm.$^{-1}$ in dilute solution in carbon tetrachloride (NH_2 group), no band was present in the region 2,300 to 2,100 cm.$^{-1}$ (-CN absent). In IIId strong bands at 1,720 and 1,680 cm.$^{-1}$ can be assigned to the ring and α,β unsaturated ester carbonyl groups. The n.m.r. spectrum ($CDCl_3$) of IIId showed the expected ethyl ester (quartet c. 6.0 τ (2H), triplet c. 9.0 τ(3H)) and aromatic proton (multiplet 2.0τ to 2.8 τ (9H)) signals and the low broad signal (3.7 to 4.7 τ (2H)) of the amino group. No signal was present near 6.5 τ ($NC-\overset{|}{C}\underline{H}-COOEt$). The ultraviolet spectrum of IIId was consistent with the ψ-indoxyl structure (17) λ_{max} (ethanol), 220mμ (ϵ , 14,700), 357mμ (ϵ , 9,350) and 313mμ (ϵ , 2,780).

These Δ^4-isoxazolines are presumably formed via the N-hydroxyindolin-3-ones (II; R = NC-$\overset{|}{C}$H-COOEt) by the well established intramolecular attack on the cyanide group by the hydroxylamino group (8). Isoxazolines previously reported in the literature (9-11,13) have where possible existed as the more stable tautomeric isoxazoles. Isoxazolines unable to tautomerise to isoxazoles are very rare (11,12).

Although isoxazolidines have been prepared from isatogens by the reaction with ethylenic compounds (5), the reaction with acetylenic compounds was anomalous leading to quinolines (6). Nitrones have been described as showing little reactivity towards weak nucleophiles (19), no reaction occurred, under these mild conditions, between α,N-diphenylnitrone and ethyl cyanacetate. Other nitrones are being investigated. The isoxazolines (III, a-d) are as expected (18) reactive compounds being attacked by both strong acids and alkali and being hydrogenated under mild conditions. Irradiation with U.V. light and heating in an inert solvent yields a variety of products. These reactions are being investigated.

References

1. R. Danieli and G. Maccagnani, Boll.sci.Fac.Chim.ind. Bologna, **23**, 347 (1965)
2. R. Danieli and G. Maccagnani, ibid, **23**, 353 (1965)
3. R. Danieli and G. Maccagnani, ibid, **23**, 405 (1965)
4. W.E. Noland and D.A. Jones, J.Org.Chem., **27**, 341 (1962)
5. W.E. Noland and D.A. Jones, Chem.Ind., 363 (1962)
6. W.E. Noland and D.A. Jones, J.Amer.Chem.Soc., **86**, 2086 (1964)
7. R. Huisgen, Angew.Chem.Int.Ed., **2**, 565 (1963)
8. L. Bauer and C.N.V. Nambury, J.Org.Chem., **26**, 4917 (1961)

9. C.J. Bell, C.N.V. Nambury and L. Bauer, J.Org.Chem., 26, 4923 (1961)

10. F. Leonard and K. Underheim, Chem.Abs., 565c (1965)

11. A.J. Boulton, A.R. Katritzky, A. Majid Hamid and S. Okone, Tetrahedron, 20, 2835 (1964)

12. S.D. Sokolov and N.K. Kochetov, Dokl.Acad.Nauk S.S.S.R., 156, 1391 (1964)

13. T. Takemoto, T. Nakajima and T. Yokobe, Yakugaku Zasshi 84, 1232 (1964)

14. W.C. Sumpter and F.M. Miller, Heterocyclic Compounds with Indole and Carbazole Systems, Chap. 5. Interscience Publishers, Inc., New York and London (1954)

15. R.T. Coutts, M. Hooper and D.G. Wibberley, J.Chem.Soc., 5205 (1961)

16. D.A. Patterson and D.G. Wibberley, J.Chem.Soc., 1706 (1965)

17. A.I. Scott, Interpretation of the Ultraviolet Spectra of Natural Products, p. 175. Pergamon Press, London (1964)

18. A.R. Katritzky, Ed., Advances in Heterocyclic Chemistry Vol. II, p. 418. Academic Press, New York and London (1963)

19. A.K. Qureshi and B. Sklarz, J.Chem.Soc.(C), 412 (1966)