direct recoil of fission fragments into organic solutions through neutron irradiation of 1-2 ml. samples in quartz tubes internally coated with 1.67 mg. of U_3O_8, and have observed organically bound fission product radioactivity afterward.

After irradiation for 12–24 hours in a neutron flux of 1–2 × 10^{12} n./cm.^{2}/sec., more than 50% of the mass 131 atoms recoiling into a benzene solution can be isolated readily as iodobenzene-I^{131}. Molecular iodine and iodobenzene carriers and additional benzene were added to each irradiated sample, and the inorganic iodine was extracted into aqueous sulfite solution. The organic phase, with added naphthalene, was distilled at atmospheric pressure using a 12″ column packed with glass rings. From one such iodobenzene fraction, one aliquot was counted directly and two others were used to form appropriate derivatives, which were then recrystallized to constant radioactivity, as shown in Table 1. The half-life and gamma ray spectrum of each aliquot showed no radioactivities other than I^{131}.[4] The constant specific activity per iodobenzene equivalent shown in the last column of Table I demonstrates that the I^{131} is actually chemically bound as iodobenzene.

TABLE I

I^{131} RADIOACTIVITY IN IODOBENZENE AND IN TWO DERIVATIVES[a]

	Weight, g.	C.p.m.	C.p.m./g. iodobenzene equivalent
Iodobenzene	8.86	1910 ± 20	216 ± 2
1-Bromo-4-iodobenzene	4.17	662 ± 7	220 ± 3
4,4′-Diiododiphenyl sulfone	1.36	272 ± 5	227 ± 4

[a] Total iodobenzene carrier = 36.6 g.

The yields of inorganic I^{131} and of alkyl iodide-I^{131} also have been determined. Carrier ethyl iodide was added to the b.p. 185° distillation fraction and then converted to silver iodide with ethanolic silver nitrate solution. The inorganic iodine was also measured as silver iodide. The relative yields of each from two separate experiments are shown in Table II.

TABLE II

OBSERVED YIELDS OF DIFFERENT I^{131}-LABELED SPECIES FROM FISSION RECOIL INTO BENZENE SOLUTION[a]

Flux, n./cm.^{2}/sec.	1.0 × 10^{12}	2.0 × 10^{12}
Hours of irradiation	24	12
Calculated yield of I^{131} recoiling into solution (d.p.m.)	1.2 × 10^6	1.2 × 10^6
Yields (d.p.m.)		
Iodobenzene	8.0 × 10^5	6.0 × 10^5
Inorganic iodine	2.4 × 10^5	4.3 × 10^5
Alkyl iodides, b.p. less than 185°	....	0.6 × 10^5

[a] All activities have been corrected for chemical yield and for decay since the end of irradiation.

Since I^{131} is formed in the primary fission process in negligibly small yields, the original mass 131 atom recoiling into the benzene solution will be Sn^{131}, Sb^{131}, or Te^{131}, and the I^{131} will subsequently be formed in the solution through the beta plus gamma decay of Te^{131} and Te^{131m} in whatever chemical forms tellurium isotopes exist in this solution. Most of the decay chains will reach I^{131} while the sample is still undergoing irradiation, and the possible mechanisms for formation of the labeled iodobenzene will include reactions not only with the stable radiation damage molecules, but with the steady state concentrations of more reactive chemical entities.

Similar experiments with other solvents have always shown volatile, organically bound I^{131} activity; as yet, their chemical identity and percentage yields of radioactivity have not been determined. Evidence also has been obtained for partial organic incorporation of antimony and tellurium fission isotopes, but without substantial radioactivity in any identified compound.

Further experiments are also in progress involving the carrier-free separation of iodobenzene-I^{131}, and an estimate of the limits on specific and total radioactivity obtainable by this method of synthesis.

These experiments reported here suggest that convenient radiation-induced syntheses of many I^{131}-labeled molecules can be obtained through proper choice of the organic solvent used in the irradiation tubes. Further work will be necessary to show whether any of the other fission isotopes can be similarly incorporated in useful amounts. The experiments also suggest that the direct utilization of fission recoil energy for radiation synthesis of unlabeled molecules will normally be accompanied by the formation of highly-radioactive organic molecules, with both the advantages and disadvantages that this will bring.

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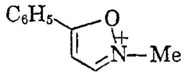
RECEIVED DECEMBER 30, 1960

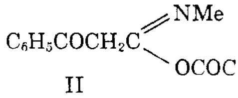
THE REACTION OF ISOXAZOLIUM SALTS WITH BASES

Sir:

In 1902, Mumm[1] made the striking observation that the N-methyl-5-phenylisoxazolium cation (I) reacts with extraordinary facility with acetate ion.



I



$C_6H_5COCH_2C(=NMe)OCOCH_3$

II

When the reaction was carried out in aqueous solution at room temperature, a crystalline substance precipitated in a few minutes. The product was formulated as the iminoanhydride (II). Subsequent studies revealed that isoxazolium salts react with similar great ease with a wide variety of carboxylates, and other nucleophiles.[2] It has been as-

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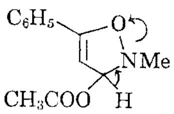
chromium hexacarbonyl recently have been investigated by F. Bäumgartner and P. Reichold, in a paper presented to the I.A.E.A. Symposium on Chemical Effects of Nuclear Transformations, Prague, October, 1960.

(4) The experiments to date have always involved search for antimony isotopes of shorter half-life, as well as iodine, in organic combination. As a result, the iodobenzene fraction has not been isolated until after the other iodine radioactivities have already decayed away.

(1) O. Mumm, "Dissertation," Kiel, 1902.

(2) K. Meyer, "Dissertation," Kiel, 1903; G. Münchmeyer, "Dissertation," Kiel, 1910; C. Bergell, "Dissertation," Kiel, 1912; A. Wirth, "Dissertation," Kiel, 1914; W. Stülcken, "Dissertation,"

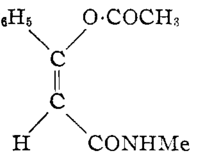
sumed[3] that these remarkable reactions proceed through the intermediacy of a pseudo base (III);



III

we may note that from the vantage point of the present day, the second stage (*cf.* III, *arrows*) of the suggested path is one for whose ready activation it is difficult to discern a justifiable basis in principle or analogy.

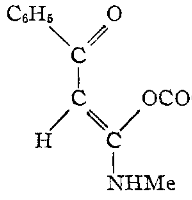
We have verified that N-methyl-5-phenylisoxazolium methosulfate reacts rapidly with sodium acetate in aqueous solution to give an almost quantitative yield of a *product*, $C_{12}H_{13}O_3N$. This substance must now be formulated as (IV). Its infrared spectrum [CH_2Cl_2] (V) is confirmatory of all of the groupings shown in (IV), while its ultraviolet spectrum [λ_{max} (ϵ), CH_2Cl_2: 267 mμ (18,700)] is entirely consistent with (IV) [*cf.* cinnamamide[4] (EtOH): 269 mμ (24,000)] but excludes the alternative structures (II), (VI) and (VII); thus, the absorption of (II) must parallel that of acetophenone[5] [242 mμ (12,000), 280 (1,000) (EtOH)], while (VI) and (VII) should absorb at considerably longer wave lengths than that observed.[6] It may be assumed with confidence that tautomeric enolic modifications corresponding to (VI) and (VII) would be unstable relative to the carbonyl forms (*cf.* $\overset{\text{OH}}{\overset{|}{-\text{C}}}{=}\text{N}-$ *vis-à-vis* $\overset{\text{O}}{\overset{\|}{-\text{C}}}-\text{NH}-$). The *cis* relationship of the acyloxy and amide groupings in (IV) is demonstrated by the ready spontaneous conversion of (IV), in ethanol solution [$t_{1/2}$ ~ 12 min. at 30°], to the N-acyl compound (VIII). The ultraviolet spectrum [242 mμ (12,300), 314 (5,100)-some enol present!; (EtOH)] of the latter parallels that of acetophenone,[5] while the infrared spectrum possesses a broad band at 5.88 μ, and no band in the NH/OH region. When (VIII) is heated in ethanol, it is cleaved to N-methylacetamide and ethyl benzoylacetate. It is noteworthy that (IV) can be recrystallized from inert solvents such as benzene without conversion to (VIII).



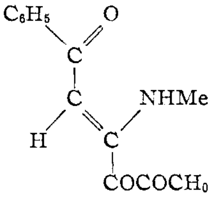
IV

2.88μ	—CONH—
5.65	—C=C—O—CO—
5.96	—CONH—
6.12	—C=C—CONH—
6.60	—CONH—
8.40	—C=C—O—CO—

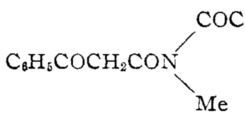
V



VI



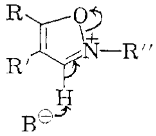
VII



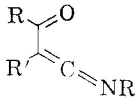
$C_6H_5COCH_2CON(COCH_3)Me$

VIII

We encountered the little-known investigations of Mumm and his collaborators in following up our hypothesis that isoxazolium salts bearing a hydrogen atom at C.3 should be converted by bases (*cf.* IX, *arrows*) to α-ketoketenimines (X). The correctness of that view has now been demonstrated by the observation that a solution of N-ethyl-5-phenylisoxazolium fluoroborate [m.p. 100–100.5°; Found: C, 50.74; H, 4.85; N, 4.92] in methylene chloride, when treated with triethylamine, *instantaneously* develops a strong infrared absorption band in the cumulated double bond region, at 4.85 μ. The band disappears very rapidly when the solution is treated with acetic acid, and the enol ester (IV) is produced. Solutions of the α-ketoketenimine undergo slow spontaneous decomposition, presumably in consequence of dimerization, or reaction with solvent impurities.

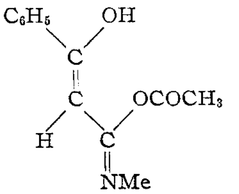


IX



X

It is now clear that the initial reaction between the isoxazolium cation (I) and acetate ion leads to the α-ketoketenimine (X: R = C_6H_5, R′ = H, R″ = Me). The combination of the latter with acetic acid to give the enol ester (IV) must involve an intermediary stage. We suggest that an initial reaction produces (XI)



XI

the latter then tautomerizes to (VI), which rearranges rapidly to (IV).

The very interesting stereoelectronic aspects of these reactions, and other details, cannot be discussed here, but the following experimental observations may be recorded: (i) when N-ethyl-5-phenylisoxazolium-3′-sulfonate[7] is recovered from

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Kiel, 1935; H. Hornbardt, "Dissertation," Kiel, 1937; L. Claisen, *Ber.*, **42**, 59 (1909); O. Mumm and G. Münchmeyer, *ibid.*, **43**, 3335 (1910); O. Mumm and C. Bergell, *ibid.*, **45**, 3040, 3149 (1912); A. Knust and O. Mumm, *ibid.*, **50**, 563 (1917); O. Mumm and H. Hornhardt, *ibid.*, **70**, 1930 (1937).

[3] E. P. Kohler and A. H. Blatt, *J. Am. Chem. Soc.*, **50**, 1217 (1928); E. P. Kohler and W. F. Bruce, *ibid.*, **53**, 644 (1931).

[4] G. Tsatsas, *Bull. soc. chim. France*, 1011 (1947).

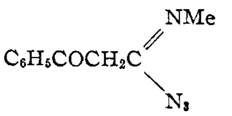
[5] R. P. Mariella and R. R. Raube, *J. Am. Chem. Soc.*, **74**, 521 (1952).

[6] For appropriate models, *cf.* K. Bowden, E. A. Braude, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 45 (1946); K. Bowden, E. A. Braude and E. R. H. Jones, *ibid.*, 945, 948 (1946); E. R. H. Jones, T. Y. Shen and M. C. Whiting, *ibid.*, 236 (1950).

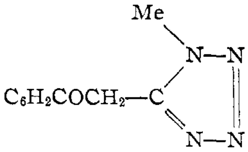
[7] R. B. Woodward, R. A. Olofson and H. Mayer, *J. Am. Chem. Soc.*, **83**, 1010 (1961).

an incomplete reaction with triethylamine in heavy water, it contains no deuterium; (ii) the product (IV: Et in place of Me) from the reaction of N-ethyl-5-phenylisoxazolium fluoroborate with sodium acetate in heavy water contains only a small and variable amount of deuterium bound to carbon; (iii) the rate of the reaction of acetic acid with the α-ketoketenimine (X: R = C_6H_5, R′ = H, R″ = Et) in methylene chloride is depressed by addition of triethylamine.

The reactions of many other nucleophiles with isoxazolium salts[2] all receive ready rationalization in terms of the initial production of α-ketoketenimines. The great facility of the reactions is dramatically illustrated by the rapid combination of (I) with azide ion in aqueous solution to give (XII) (Found: C, 59.30; H, 5.06; N, 28.18)


$C_6H_5COCH_2C\begin{matrix} /\!\!/ \, NMe \\ \diagdown \, N_3 \end{matrix}$

XII



XIII

[infrared spectrum (CH_2Cl_2)—4.69 μ, 5.90, 6.17; ultraviolet spectrum (EtOH)—348 mμ (6,000), 285(1,500), 245 (12,500)]. This substance is the only known simple iminoazide[8]; in hydroxylic solutions it cyclizes readily [$t_{1/2} \sim 100$ min. in $MeOH/H_2O$: 1/1 at 27°] to the isomeric tetrazole (XIII)[9] [infrared spectrum (CH_2Cl_2)—5.90 μ; ultraviolet spectrum (EtOH)—285 mμ (1,600), 245(14,200)], which is hydrolyzed by hot 2 *N* sodium hydroxide to benzoic acid and 1,5-dimethyltetrazole, identical with an authentic sample.[10]

The reaction of the N-methyl-5-phenylisoxazolium cation (I) with acetate ion to give the enol ester (IV) exemplifies a process for converting a carboxylate group into a reactive ester group by a very rapid and smooth reaction, occurring under conditions of exceptional mildness. The adaptation of the reaction for use in a new method of peptide synthesis is described in an accompanying communication.[7]

We wish to express our appreciation of support by the National Science Foundation and the National Institutes of Health.

[8] *Cf.* J. H. Boyer and E. J. Miller, Jr., *J. Am. Chem. Soc.*, **81**, 4671 (1959).

[9] This substance was isolated, but described as having a different structure, by W. Stülcken, ref. 2.

[10] *Cf. Chem. Abs.*, **26**, 2199 (1932).

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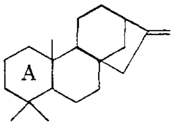
RECEIVED JANUARY 13, 1961

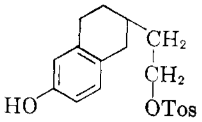
SYNTHESIS OF 4a,6-ETHANO-5.6 7,8-TETRAHYDRO-2(4a)-NAPHTHALENONE

Sir:

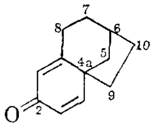
Recent investigations[1] have shown that the bicyclo[3,2,1]octane system is a structural unit common to a number of diterpene alkaloids and diterpenes, *e.g.*, phyllocladene (I). We have searched for a general approach to the synthesis of these compounds and wish to report the successful conversion of 6-hydroxy-2-(β-tosyloxyethyl)-1,2,3,4-tetrahydronaphthalene (II) to the compound in the title.



I



II



IV

Winstein and Baird[2a] first observed the conversion of *p*-(ω-tosyloxybutyl)-phenol (III) to spiro-(4,5)-deca-1,4-diene-3-one through so-called Ar_1 5 participation. Since then only a few examples of this type of reaction have been recorded[2b] and the application has been limited to simple *p*-substituted phenols.

Refluxing a dilute (0.01 *M*) solution of II in *tert*-butyl alcohol with a slight excess of potassium *t*-butoxide for six hours afforded in approximately 90% yield a colorless liquid,[3] $n^{26}\mathrm{D}$ 1.5738 (found: C, 82.75, H, 8.17) $\lambda_{\max}^{\mathrm{MeOH}}$ 246 mμ (ϵ 1.57 × 10^4) $\lambda_{\max}^{\mathrm{Chl}}$ 6.02 μ, 6.17, 6.22 (shoulder); semicarbazone, m.p. 222–224° (found: C, 67.71, H, 7.52). In view of the elementary analyses and spectral evidence, this liquid is represented by formula IV. The yield appeared to be the highest ever reported for this type of reaction. Undoubtedly this smooth cyclization was effected by an advantageous orientation of the carbon atom carrying the tosylate group. Side reactions are suppressed by the tertiary C_6 atom, a structural feature not present in III.

Preparation of II.—The Reformatsky reaction of 6-methoxy-β-tetralone[4] with ethyl bromoacetate produced a β-hydroxy ester (V), b.p. 174–175° (0.75 mm.) (found: C, 66.73, H, 7.75). The ester (V) was dehydrated with thionyl chloride and pyridine to an unsaturated ester (VI), b.p. 135–137° (0.09 mm.) (found: C, 72.90, H, 7.60). The unsaturated ester was reduced catalytically to afford ethyl 6-methoxy-1,2,3,4-tetrahydronaphthalene-2-acetate (VII),[5] b.p. 127–128° (0.06 mm.), which was reduced with lithium aluminum hydride to the corresponding alcohol (VIII), b.p. 132–133° (0.07 mm.) (found: C, 75.81, H, 9.00). Pyrolysis of the methylmagnesium iodide complex of VIII at 175° effected demethylation,[6] affording a hydroxy phenol (IX), m.p. 88–90° (found: C, 75.12, H, 8.21). The phenol (IX) was converted to II[7] through the benzyl ether (X), m.p. 61–62° (found: C, 81.17, H, 7.82) and the benzyl ether tosyl ester (XI) m.p. 76–78° (found: C, 71.52, H, 6.50). Catalytic hydrogenolysis of XI with palladium on carbon proceeded without difficulty.

[1] For instance, see: K. Wiesner and Z. Valenta, *Fortschr. Chem. org. Naturstoffe*, **16**, 26 (1958); L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmshurst, *Tetrahedron Letters*, No. 8, 8 (1959).

[2] (a) S. Winstein and R. Baird, *J. Am. Chem. Soc.*, **79**, 756 (1957). (b) S. Doring and J. Harley-Mason, *Chem. and Ind.*, 1551 (1959), and references cited therein.

[3] This liquid was purified by silicic acid chromatography, then evaporative distillation at 60° (0.1 mm.).

[4] N. A. Nelson, R. S. P. Hsi, J. M. Shuck and L. D. Kahn, *J. Am. Chem. Soc.*, **82**, 2573 (1960).

[5] The corresponding acid melts at 91–92° (found: C, 71.02, H, 7.13).

[6] W. S. Johnson, E. R. Rogier and J. Ackerman, *ibid.*, **78**, 6322 (1956).

[7] II was sensitive to air oxidation and resisted crystallization. Purification was achieved by silicic acid chromatography.