block polymer is established. Many other block polymers were prepared by this technique.

The naphthalene–sodium initiator gives block polymers of the type A·B·A, or A·B·C·B·A.[6] The presence of two living ends was proved by experiments which will be reported later. However, the same method can be applied to conventional initiators of anionic polymerization yielding block polymers of the type A·B· or A·B·C.

(6) In these and in the following formulas letter A, B and C stand for blocks of monomers, *i.e.*, A....A, B....B, or C....C.

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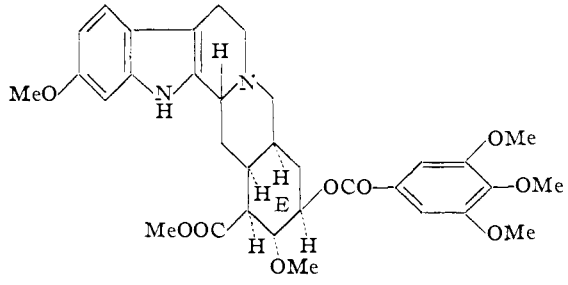
RECEIVED MARCH 29, 1956

A SIMPLIFIED ROUTE TO A KEY INTERMEDIATE IN THE TOTAL SYNTHESIS OF RESERPINE

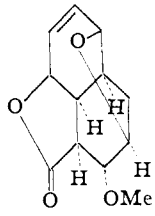
Sir:

Recently we recorded[1] the total synthesis of reserpine (I), through a route involving the meth-

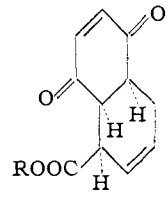


I

oxy-ether (II), which was prepared from the *p*-benzoquinone–vinylacrylic acid adduct (III, R = H) by a five-stage process. We now wish to report



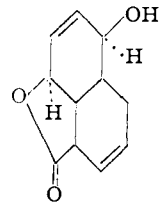
II



III

that the key intermediate (II), *which contains all five of the asymmetric carbon atoms of Ring E of reserpine, properly oriented,* is readily preparable from the *p*-benzoquinone–methyl vinylacrylate adduct (III, R = Me) in two simple operations.

The adduct (III, R = Me) (m.p. 103–104°, found: C, 65.07; H, 5.57), from *p*-benzoquinone and methyl vinylacrylate in benzene, was smoothly converted by aluminum isopropoxide in hot isopropyl alcohol to the hydroxylactone (IV) (m.p. 122–123°, found: C, 68.79; H, 6.50), which with bromine in methanol, followed by sodium methoxide, gave the methoxylactone (II).



IV

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RECEIVED APRIL 19, 1956

INVESTIGATION OF SYNTHESIS *VERSUS* REËNTRY IN TWO ORGANIC NITROGEN CONTAINING SYSTEMS UNDER NEUTRON IRRADIATION[1]

Sir:

Previous work by the authors[2] has shown that both anthracene-C^{14} and acridine-C^{14} are produced by the neutron irradiation of acridine. These products are formed by *reëntry*[3] of the recoiling carbon-14 which travels a considerable distance after being "born."[4]

It became increasingly evident from our work on this and other systems that the inordinate difficulty in bringing the products to radiochemical purity was possibly due to *synthesis*[5] products which were difficult to remove because of their presence in the parent compound. In most cases it would be reasonable to expect their chemical behavior to be similar to that of the parent compound. Trace degradation products may also be important.

We have irradiated benzene in 2-methylpyrazine, and acetamide, in the Brookhaven Reactor. The presence of two possible *synthesis* products, toluene and propionamide, were then investigated by carrier methods.

In the case of acetamide, both propionamide and propionic acid were added as carriers on the assumption that the synthesized, excited three carbon fragment might in some cases collapse to give propionic acid. The hydrolysis was carried out both in acid and base to investigate possible differences in the state of the irradiated material. Degradations were carried out by the method of Phares.[6] The results are given in Tables I and II.

While it is clear from these results that *synthesis* does take place, *it becomes evident that the reaction to give toluene or propionamide involves processes other than a simple displacement* by a "hot" methyl radical.[7] The activity in the methylene, carboxyl, and ring carbons of the carrier materials studied cannot be credited to an inversion[8] reaction, al-

(1) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, THIS JOURNAL, **78**, 2023 (1956).

(1) Research performed under the auspices of the U. S. Atomic Energy Commission.

(2) A. P. Wolf and R. C. Anderson, THIS JOURNAL, **77**, 1608 (1955).

(3) We prefer *reëntry* to retention in describing this process in order to avoid the implication, in the case of anthracene, that the molecule containing the N^{14} undergoing nuclear transformation is the same molecule which then contains the C^{14} in its ring.

(4) W. F. Libby, THIS JOURNAL, **69**, 2523 (1947); H. Faraggi, *Ann. Phys.*, **6**, 325 (1951).

(5) By *synthesis* we mean any product formed which has *one carbon more* than the parent compound exclusive of the carbon analog of the parent compound. See also A. G. Schrodt and W. F. Libby, THIS JOURNAL, **76**, 3100 (1954); L. J. Sharman and K. J. McCallum, *ibid.*, **77**, 2989 (1955).

(6) E. F. Phares, *Arch. Biochem. Biophys.*, **33**, 173 (1951).

(7) J. E. Willard, *Ann. Rev. Phys. Chem.*, **6**, 141 (1955).

(8) J. F. Hornig, G. Levey and J. E. Willard, *J. Chem. Phys.*, **20**, 1556 (1952).

TABLE I

ACETAMIDE

Compound	Basic hydrolysis[a] CH_3——COOH		Basic hydrolysis[a] CH_3——CH_2——COOH			Acidic Hydrolysis[b] CH_3——COOH		Acidic Hydrolysis[b] CH_3——CH_2——COOH		
1 Specific activity, mμc./mg. C	0.539	0.840	3.30	1.44	1.49	0.886	1.520	1.496	0.759	0.573
2 Per cent. of summed activity by position	39.1	60.9	52.9	23.1	23.9	36.9	63.1	52.9	26.8	21.0
3 Specific activity, assay on compd.	0.715[c]		2.18[d]			1.24[c]		1.01[d]		
4 Activity accounted for by degradation, %	95.8		95.4			96.8		93.5		
5 Activity relative to total activity in irradiated sample, %	6.44		6.69			8.12		5.00		

[a] 4965 megawatt hr. irradiation of acetamide. [b] 6254 megawatt hr. irradiation of acetamide. [c] Neat. [d] Carrier material.

TABLE II

BENZENE + 2-METHYLPYRAZINE[a]

Compound	C_6H_5——CH_3		C_6H_6[b]
1 Specific activity, mμc./mg. C	0.024	1.01	0.068[c]
2 Per cent. of activity summed by position	13.9	86.1	
3 Specific activity, assay on compd.	0.173[d]		
4 Activity relative to total activity in irradiated sample, %	1.05		1.92

[a] 2404 megawatt hr. irradiation of mixture. [b] *Cf.* A. P. Wolf, C. S. Redvanly and R. C. Anderson, *Nature*, 176, 831 (1955). [c] This is an upper limit. [d] Carrier material.

though most of the activity in the methyl group may arise by this path. A possible mechanism for formation of *synthesis* products would involve the inelastic collision of fragments such as CH_3· or CH_2:, having energies in excess of 0.5 e.v. but not above 10 e.v., with the molecules in question. In this way, propionamide with the methylene carbon active might be formed by the insinuation of CH_2: between the methyl and carbonyl carbon. Unstable three carbon intermediates leading to partial equilibration of the three positions in propionamide may also be possible precursors. Malonic and succinic acids produced by hot atom and radiation chemical processes could ultimately lead to acetic acid and propionic acid. Note the higher activity yield in acetic acid for the acid hydrolysis.

Since the material is produced in a strong radiation field,[9] one must also consider the possibility of radical recombinations in and around any radiation damage or recoil track leading to these products. We hope that experiments underway at present may distinguish between these pathways.

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RECEIVED MARCH 27, 1956

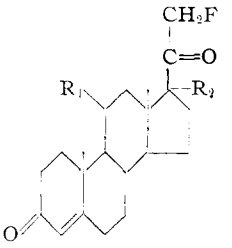
(9) Thermal neutron flux ≅ 4 × 10^{12} neutrons/cm.² sec.; fast neutron flux ≅ 10^{12} neutrons/cm.² sec.; gamma exposure ≅ 5 × 10^6 *r*/hr.

(10) Guest Associate Chemist, Brookhaven National Laboratory, Fall, 1955, from Martinez Research Laboratory, Shell Oil Co., Martinez, California.

THE PREPARATION OF 21-FLUOROSTEROIDS

Sir:

In connection with the search for compounds useful in the regulation of endocrine balance,[1] we have prepared the 21-fluorinated analogs of a number of steroid hormones by a convenient procedure of general applicability. Such products show promise of interesting physiological properties.



	R_1	R_2
III	H_2	H
IV	OH, H	H
V	=O	OH
VI	OH, H	OH

When a 21-iodosteroid dissolved in moist acetonitrile is treated with a slight excess of a 50% aqueous solution of silver fluoride[2] at 30 to 40°, a precipitate of silver iodide soon separates leaving the fluorosteroid in solution. In this way 21-iodo-5-pregnen-3β-ol-20-one acetate, prepared by the action of N-iodosuccinimide on 5,20-pregnadiene-3β,20-diol diacetate,[3] was converted in 45% yield to 21-fluoro-5-pregnen-3β-ol-20-one acetate (I), m.p. 155–156°, $[\alpha]^{25}D$ +32° ($CHCl_3$); *Anal.* Calcd. for $C_{23}H_{33}O_3F$: C, 73.37; H, 8.83; F, 5.04. Found: C, 72.78; H, 8.73; F, 5.17. Treatment of I with 1% methanolic hydrogen chloride at room temperature gave 85% of 21-fluoro-5-pregnen-3β-ol-20-one (II), m.p. 178.5–179.5°, $[\alpha]^{25}D$ +25° ($CHCl_3$); *Anal.* Calcd. for $C_{21}H_{31}O_2F$: C, 75.41; H, 9.34; F, 5.68. Found: C, 75.56; H, 9.34; F, 5.59.

By an analogous reaction with aqueous silver fluoride in acetonitrile, 21-iodoprogesterone, prepared by the action of sodium iodide on desoxycorticosterone methanesulfonate,[4,5] was converted in 63% yield to 21-fluoroprogesterone (III), m.p. 141.5–142.2°, $[\alpha]^{25}D$ +208 ($CHCl_3$); *Anal.* Calcd. for $C_{21}H_{29}O_2F$: C, 75.87; H, 8.79; F, 5.72. Found: C, 75.83; H, 8.92; F, 5.77. Similarly, corticosterone 21-methanesulfonate was transformed, *via* the 21-iodosteroid, to 21-fluoro-11β-hydroxyproges-

(1) T. C. Myers, R. J. Pratt, R. L. Morgan, J. O'Donnell and E. V. Jensen, THIS JOURNAL, **77**, 5655 (1955).

(2) The use of anhydrous silver fluoride in dry acetonitrile has been employed for the fluorination of α-acetobromoglucose: B. Helferich and R. Gootz, *Ber.*, **62**, 2505 (1929).

(3) C. Djerassi and C. T. Lenk, THIS JOURNAL, **75**, 3493 (1953).

(4) The 21-methanesulfonate esters of desoxycorticosterone, corticosterone, cortisone and hydrocortisone were prepared by treatment of the 21-hydroxysteroids with methanesulfonyl chloride and pyridine according to the procedure of J. Fried (private communication).

(5) The preparation of 21-iodosteroids by the action of sodium iodide on the corresponding 21-*p*-toluenesulfonate esters has been described recently: P. Borrevang, *Acta Chem. Scand.*, **9**, 587 (1955).