of ribonuclease, of the 664 non-exchangeable hydrogens 7.1% are aromatic and 45.0% are on aliphatic carbon atoms attached only to other aliphatic carbons. Of the remaining protons, 19.0% are on α carbons, 8.1% are on carbons attached to carboxyls and amides, 6.0% are on carbons with hydroxyl substituents, 5.4% are on carbons attached to sulfur, 4.2% are on carbons bonded to positively charged nitrogen, 3.9% are on carbons attached to aromatic nuclei, and 1.2% are on carbons bound to amide nitrogen. All of these categories could reasonably be expected to give rise to peaks between the extremes, but their positions in peaks II and III cannot be assigned with certainty at this time.

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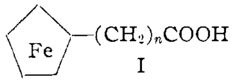
FERROCENE BRIDGING AND HOMOANNULAR CYCLIZATIONS[1]

Sir:

The question of homoannular *vs.* heteroannular intramolecular acylation in substituted ferrocenes has been raised recently by Nesmeyanov.[2] We wish to report here examples of both of these types of cyclizations from suitable ω-ferrocenylaliphatic acids[3] (I), together with an instance of intermolecular acylation, and to present evidence that the product obtained from these ferrocenyl aliphatic acids is determined by the length of the polymethylene chain separating the ferrocene nucleus from the carboxyl group.



I

β-Ferrocenylpropionic acid[3] (Ia, $n = 2$), when treated with polyphosphoric acid, gave heteroannular cyclization to the bridged compound 1,1′-(α-ketotrimethylene)-ferrocene,[4] m.p. 144–144.5°.[5] *Anal.* Calcd. for $C_{13}H_{12}FeO$: C, 65.03; H, 5.04; Fe, 23.26; mol. wt., 240. Found: C, 64.50; H, 5.04; Fe, 23.98; mol. wt. 281 (ebull., benzene), 324 (ebull., butanone). The infrared spectrum contains ketone bands at 1682 and 1266 cm.$^{-1}$, but no bands near 1110 or 1004 cm.$^{-1}$. Presence of 1110 and 1004 cm.$^{-1}$ bands would indicate an unsubstituted cyclopentadienyl ring.[3,6] The ultraviolet spectrum of this ketone is highly characteristic in that it shows no maximum near 225 or 270 mμ, regions where maxima have been shown to occur for ketones conjugated with the ferrocene nucleus.[7] Such spectral behavior is reasonable for a compound of this structure since the stereochemistry of the 3-carbon bridge prevents coplanarity, and thus conjugation, of the carbonyl with the adjacent ring.

γ-Ferrocenylbutyric acid[3] (Ib, $n = 3$), when treated with either polyphosphoric acid or trifluoroacetic anhydride, gave as the major product the homoannular cyclized ketone, 1,2-(α-ketotetramethylene)-ferrocene,[8] m.p. 85.4–85.7°, λ_{max} 226, 270 mμ, ϵ_{226} 17,600, ϵ_{270} 7,500, infrared bands: 1679, 1281, 1109, 1003 cm.$^{-1}$. *Anal.* Calcd. for $C_{14}H_{14}FeO$: C, 66.19; H, 5.55; mol. wt., 254. Found: C, 66.59; H, 5.69; mol. wt., 286 (ebull., butanone).

δ-Ferrocenylvaleric acid[3] (Ic, $n = 4$), with either polyphosphoric acid or trifluoroacetic anhydride, gave the homoannular product, 1,2-(α-ketopentamethylene)-ferrocene, m.p. 65.5–66.5°, λ_{max} 227, 269 mμ, ϵ_{227} 15,500, ϵ_{269} 7,400, infrared bands: 1655, 1290, 1110, 1004 cm.$^{-1}$. *Anal.* Calcd. for $C_{15}H_{16}FeO$: C, 67.19; H, 6.02; mol. wt., 268. Found: C, 66.99; H, 6.18; mol. wt., 314 (ebull., butanone). The shift in the infrared carbonyl band to lower frequency[9] and the reduction in the extinction coefficient in the ultraviolet spectrum,[10] when compared to similar spectral features of the lower, homologous, ketone from IIb, containing a 6-membered ring, are in agreement with like shifts found between the corresponding 7- and 6-membered benzocyclanones.[9,10]

The principal product from the treatment of ε-ferrocenylcaproic acid[3] (Id, $n = 5$) with polyphosphoric acid was a red-brown solid, apparently polymeric,[11] insoluble in usual organic solvents, decomposing slowly above 200°. The material exhibits strong infrared ketonic absorption (1660 cm.$^{-1}$), weaker carboxyl absorption (1725, 2700, 2620 cm.$^{-1}$) and gives analytical data consistent with those for a condensation trimer, as $H[C_{10}H_8Fe(CH_2)_5CO]_3OH$, though it is more likely a mixture of compounds of varying molecular weight. *Anal.* Calcd. for $C_{48}H_{56}Fe_3O_4$: C, 66.68; H, 6.53; Fe, 19.38. Found: C, 66.76; H, 6.58; Fe, 18.95.

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(1) Presented in part at the 131st Meeting of the American Chemical Society, Miami, Florida, April 7–12, 1957; *cf.* Abstracts, p. 46-O.

(2) A. N. Nesmeyanov, N. A. Volkenau and V. D. Vilchevskaya, *Doklady Akad. Nauk S.S.S.R.*, **111**, 362 (1956).

(3) K. L. Rinehart, Jr., R. J. Curby, Jr., and P. E. Sokol, THIS JOURNAL, **79**, in press (1957).

(4) Ferrocene substituents on the same cyclopentadienyl ring are numbered "1, 2, 3," etc., as in the benzenoid compounds, while substituents on the second cyclopentadienyl ring are indicated by an accent, as "1′, 2′, 3′," etc. [*cf.*, *e.g.*, P. L. Pauson, THIS JOURNAL, **76**, 2187 (1954)].

(5) Woodward and Csendes obtained what is apparently the same compound (m.p. 141–142°) from treatment of β-ferrocenylpropionic acid with trifluoroacetic anhydride, though the ketone was incompletely characterized (R. B. Woodward and E. Csendes, personal communication; *cf.* ref. 6, Appendix).

(6) M. Rosenblum, Ph.D. Thesis, Harvard University, August, 1953.

(7) K. L. Rinehart, Jr., K. L. Motz and S. Moon, THIS JOURNAL, **79**, 2749 (1957).

(8) Nesmeyanov[2] has recently assigned a di-homoannular structure similar to this to the polyphosphoric acid cyclization product from 1,1′-ferrocenedibutyric acid.

(9) W. M. Schubert and W. A. Sweeney, THIS JOURNAL, **77**, 4172 (1955).

(10) G. D. Hedden and W. G. Brown, *ibid.*, **75**, 3744 (1953).

(11) Homoannular cyclization of Id would require the formation of an 8-membered ring expected to form with difficulty. A similarly difficult cyclization would be anticipated from ferrocenylacetic acid[3] (I, $n = 1$), which must give either a highly strained 4-membered benzocyclobutanone ring or a 2-carbon bridge, for which the interannular distance probably is too great.[12] In preliminary experiments in polyphosphoric acid, no ketonic product has been obtained.

(12) P. F. Eiland and R. Pepinsky, THIS JOURNAL, **74**, 4971 (1952); J. D. Dunitz and L. E. Orgel, *Nature*, **171**, 121 (1953).

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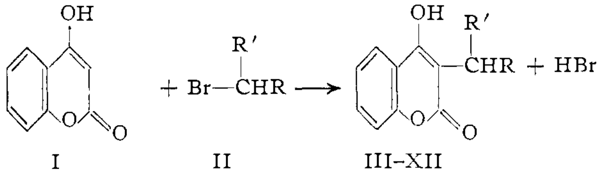
A NEW SYNTHETIC APPROACH TO SOME 3-ARALKYL-4-HYDROXYCOUMARINS[1]

Sir:

Since the introduction of the anticoagulant Dicumarol®, 3,3′-methylenbis-(4-hydroxycoumarin) for clinical purposes,[2] interest in the synthesis of new 3-substituted-4-hydroxycoumarins and in new methods of synthesizing them has been maintained. While the reactivity of the 3-position of 4-hydroxycoumarin (I) is well known,[3,4,5] the direct alkylation of the 3-position of 4-hydroxycoumarin with reactive halides under acidic conditions has not been reported. Grüssner[6] had reported the alkylation of 4-hydroxycoumarins with reactive allyl and substituted allyl bromides under alkaline conditions. This method leaves much to be desired with respect to the yields obtained (usually 10–15%) and the scope of the procedure.

Recently Grüssner and Hegedüs[7] reported a novel, mutiple-step procedure for the preparation of 3-aralkyl-4-hydroxycoumarins, in which organometal compounds are condensed with 3-acyl-4-hydroxycoumarins to form tertiary carbinols which are in turn dehydrated to the corresponding unsaturated compounds and which upon catalytic hydrogenation give the desired 3-aralkyl-4-hydroxycoumarins.

In a recent paper Ziegler and Roszmann[8] reported the synthesis of 3-substituted benzyl-4-hydroxycoumarins by condensing 4-hydroxycoumarin and substituted benzyl alcohols directly using phosphorus oxychloride as the catalyst and solvent.


I II III–XII

We have found that 4-hydroxycoumarin (I) can be alkylated readily in the 3-position by heating it in the molten state with certain reactive aralkyl halides (II) at temperatures of 130–180°. The 3-aralkyl-4-hydroxycoumarins (III–XII) are readily isolated in the pure state and usually in very good yields.

Alkylation of 4-hydroxycoumarin with certain aralkyl bromides (II) (or chlorides) in the molten state (length of heating period and temperature vary depending on the bromide used) gave 3-aralkyl-4-hydroxycoumarins (III–XII) in good yields. The physical and analytical data for the compounds reported herein are in the table.

TABLE I

3-SUBSTITUTED-4-HYDROXYCOUMARINS

	R	R′	M.p.,[a] °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
III	Phenyl[b]	H	197–200	53	$C_{16}H_{12}O_3$				
IV	*o*-Methylphenyl	H	202–206	95	$C_{17}H_{14}O_3$	76.7	76.8	5.3	5.4
V	*o*-Chlorophenyl	H	229–232	28	$C_{16}H_{11}ClO_3$	67.0	66.6	3.8	4.1
VI	Benzyl[c]	H	195–198	82	$C_{17}H_{14}O_3$				
VII	Phenyl[d]	CH_3	201–202	97[d]	$C_{17}H_{14}O_3$				
VIII	Phenyl[d,e,f]	C_2H_5	175–177	98	$C_{18}H_{16}O_3$				
IX	Phenyl[f]	*n*-C_3H_7	191–194	95	$C_{19}H_{18}O_3$				
X	Phenyl[f]	*n*-C_4H_9	179–180	97	$C_{20}H_{20}O_3$				
XI	Phenyl	*n*-C_5H_{11}	148–149	96	$C_{21}H_{22}O_3$	78.4	78.1	6.8	6.8
XII	Phenyl	Phenyl	177–178	99	$C_{22}H_{17}O_3$	80.5	80.3	4.9	5.0

[a] Melting points are uncorrected. [b] I. M. Heilbron and D. W. Hill, *J. Chem. Soc.*, 1705 (1927), report a m.p. of 205°. [c] H. Pauli and K. Lockemann, *Ber.*, **48**, 28 (1915), report a m.p. 205–206°. [d] H. Junek and E. Ziegler, *Monatsh.*, **87**, 218 (1955), report a m.p. 202° and a yield of *ca.* 10% for VII and a m.p. 175–176° for VIII. [e] F. Litvan and W. Stoll, U. S. Patent 2,647,681, Aug. 11, 1953, report a m.p. 179°. [f] A. Grüssner and B. Hegedüs (see ref. 7) report a m.p. 179–180° for VIII, a m.p. of 201–202° for IX, a m.p. 178–180° for X, no yields were reported.

Benzylation of the 3-position of 4-hydroxycoumarin by heating with benzyl *p*-toluenesulfonate[9] in the molten state at 100–120° gave 3-benzyl-4-hydroxycoumarin (III) in 15% yield.

The synthesis of some of the 3-aralkyl-4-hydroxycoumarins listed here by the older procedures would be very tedious if indeed it could be realized.[10,11] The recent method of Grüssner and

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[2] K. P. Link, *The Harvey Lecture Series*, **39**, 162 (1943–1944).

[3] M. Ikawa, M. A. Stahmann and K. P. Link, THIS JOURNAL, **66**, 902 (1944).

[4] C. F. Huebner and K. P. Link, *ibid.*, **67**, 99 (1945).

[5] H. R. Eisenhauer and K. P. Link, *ibid.*, **75**, 2044 (1953).

[6] A. Grüssner, "Jubilee Volume," F. Hoffman–La Roche and Co., Ltd., Basle, 1946, p. 238.

[7] A. Grüssner and B. Hegedüs, U. S. Patent 2,723,276, Nov. 8, 1955.

[8] E. Ziegler and U. Roszmann, *Monatsh.*, **88**, 25 (1957).

[9] J. K. Kochi and G. S. Hammond, THIS JOURNAL, **75**, 3443 (1953), report the preparation of benzyl *p*-toluenesulfonate.

[10] R. C. Elderfield, "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 174–194.

[11] H. Simonis, "Die Cumarine," Ferdinand Enke, Stuttgart, 1916, pp. 200–205.