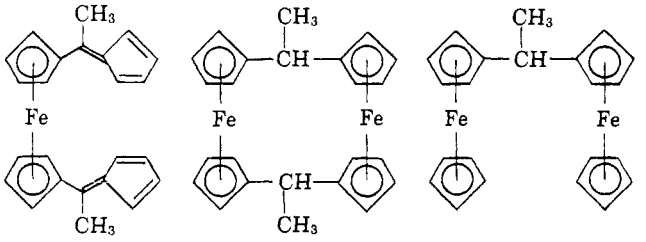


I II III

salt[5] which, on treatment with ferrous chloride, gave a mixture of products from which II was separated chromatographically in yields from 14 to 20%. The compound crystallized from ligroin in orange blades, mp 182–184° [*Anal.* Calcdf or $C_{24}H_{24}Fe_2$: C, 68.0; H, 5.7; mol wt, 424. Found: C, 68.1; H, 6.1; mol wt (mass spectrum), 424], and is assigned the structure II on the basis of the spectral characteristics summarized as follows.

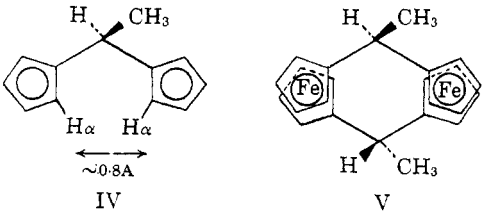
The infrared spectrum conforms to that expected of a heteroannularly substituted dialkylferrocene and, except for the absence of bands at 9 and 10 μ,[6] bears a close similarity to that of the related 1,1-diferrocenylethane (III).[7] As is generally the case with ferrocene derivatives,[8] the molecular ion peak in the mass spectrum is by far the most intense and establishes the molecular weight (for ^{56}Fe) to be 424, while the relative peak heights in the molecular ion group demonstrate the presence of two iron atoms. Two successive losses of methyl groups are indicated by the appearance of groups of peaks at $(M - 15)^+$ and $(M - 30)^+$ and confirmed by the presence of the appropriate metastable peaks, and these groups together with the M^+ group have doubly charged counterparts at $m/2e$ = 212, 204.5, and 197. The subsequent cracking pattern involves loss of a cyclopentadienyl group followed by general fragmentation.

The pmr spectrum (see Table I) comprises four groups of resonances in the ratio 4:12:2:6 (field increasing). The methyl and methine protons appear as a clean doublet centered at τ 8.90 and quadruplet centred at τ 6.33 (J = 7.5 cps), respectively, showing that the two methyl groups (and also the two methine protons) occupy equivalent molecular environments. The presence of two groups of cyclopentadienyl protons appearing as complex multiplets centered at τ 5.58 and 6.02, respectively, infers that the molecule is twisted in such a way that four of the 16 ring protons lie further from the iron atoms and are thus deshielded with respect to the remaining 12.[9,10] Such molecular distortion is to be expected since a geometry involving coplanarity of the rings in each hydrocarbon ligand in parallel planes "sandwiching" the iron atoms would lead to an impossibly severe steric interaction between H_α protons (see IV).

Table I. Pmr Spectra[a]

Compd	τ_{CH_3}	τ_{CH}	τ_{ring}
II	8.90	6.33	5.58 6.02
III	8.47	6.60	6.08

[a] In CS_2 solution at 40 Mcps against TMS.



IV V

By comparison of the chemical shifts of the methyl and methine protons in II and III (see table), the ferrocenophane is tentatively assigned structure V, in which the methyl groups have the *exo* configuration. Although rotation of the ferrocenyl groups in III about the ring CH bonds would result in the chemical shift values of the methyl and methine protons, reflecting a time-averaged environment relative to the iron atoms, the upfield shift of the resonance of the methyl protons and the corresponding downfield shift of that of the methine protons in going from III to II can be best accommodated by structure V for the ferrocenophane.[11] Nonbonded interaction between methine protons render improbable the isomeric structure containing completely eclipsed ligands.

Both the fulvene route and other methods of preparation of related [1, 1]ferrocenophanes are being currently explored.

Acknowledgments. The author thanks Drs. P. Bladon and H. C. Hill for the determination of the pmr and mass spectra.

(5) Analogous fulvene reductions have been described; *cf.* G. R. Knox, J. D. Munro, P. L. Pauson, G. H. Smith, and W. E. Watts, *J. Chem. Soc.*, 4619 (1961).

(6) *Cf.* M. Rosenblum, *Chem. Ind.* (London), 953 (1958).

(7) K. L. Rinehart, Jr., P. A. Kittle, and A. F. Ellis, *J. Am. Chem. Soc.*, **82**, 2082 (1960).

(8) D. J. Clancy and I. Spilners, *Anal. Chem.*, **34**, 1839 (1962).

(9) The shielding influence of the iron atom is well documented; *e.g.*, see K. L. Rinehart, Jr., D. E. Bublitz, and D. H. Gustafson, *J. Am. Chem. Soc.*, **85**, 970 (1963).

(10) Alternatively, it could be argued that the severe steric interaction between the two pairs of H_α protons (see IV) and their unique proximity to two cyclopentadienyl rings might cause them to be specifically deshielded. The deshielding of sterically compressed protons in polycyclic benzenoid compounds has been explained on such a basis; *cf.* C. Reid, *J. Am. Chem. Soc.*, **78**, 3226 (1956); *J. Mol. Spectry*, **1**, 18 (1957).

(11) Although the region close to the iron atom is known to be strongly shielding in nature,[9] protons located in the remaining volume between the planes of the rings are deshielded in accord with the molecular diamagnetic anisotropy defined by the susceptibility measurements of L. N. Mulay and M. E. Fox, *J. Am. Chem. Soc.*, **84**, 1308 (1962); *J. Chem. Phys.*, **38**, 760 (1963). An illustrative example is provided by M. Rosenblum in "Chemistry of the Iron Group Metallocenes," Part 1, Interscience Publishers, Inc., New York, N. Y., 1965, p 217.

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A Steroidal Analgesic

Sir:

We wish to report the synthesis of a new class of analgesic compounds having poly(lower alkoxy)estrane structures. These compounds, represented by the structure 2,3,4-trimethoxyestra-1,3,5(10)-trien-17β-ol (VI), are potent analgesics. In the "rat-tail flick" method of D'Amour and Smith[1] VI, by intravenous ad-

(1) F. E. D'Amour and D. L. Smith, *J. Pharmacol.*, **72**, 74 (1941).

ministration, proved 40 and 160 times more potent than morphine sulfate and Meperidine, respectively. The acute intravenous LD_{50} of compound VI in mice was found to be 175 ± 28.6 mg/kg, and the oral LD_{50} was greater than 500 mg/kg. The acute intravenous LD_{50} in rats was 193.9 ± 31.4 mg/kg. Doses of 3–5 mg/kg administered to cats and dogs allowed abdominal surgery to be performed without further medication and with uneventful recovery. Estrogen activity as tested by the Allen and Doisy test[2] showed no activity when compared with estrone and estradiol-17β. No effect on vital signs (blood pressure, respiration, and electrocardiogram) in dogs were found as studied by the administration of compound VI in doses of 1–10 mg/kg intravenously. All pathology reports on tissues, urinalysis, and hematology were negative after chronic administration of the drug. Significantly compound VI does not cause maniacal behavior in cats. Compound VI has been successfully employed intravenously in the control of postoperative pain and chronic pain due to malignancy.[3]

The synthesis of compound VI by two different methods is described in the present communication.

In the first approach 17β-acetoxy-2-methoxyestra-1,3,5(10)-triene-3-(2′-benzoyl-4′-nitrophenyl) ether (I)[4] was allowed to react with concentrated sulfuric acid to give a deep purple solution of xanthylium acid sulfate salt (II). II was oxidized with 30% hydrogen peroxide,[5] and the crude 17β-acetoxy-4-hydroxy-2-methoxyestra-1,3,5(10)-triene-3-(2′-benzoyl-4′-nitrophenyl) ether was treated, without further purification, with diazomethane to give 17β-acetoxy-2,4-dimethoxyestra-1,3,5(10)-triene 3-(2′-benzoyl-4′-nitrophenyl) ether (III),[6] mp 114–117°, $[\alpha]^{27}D$ −10.5° ($CHCl_3$), λ_{max}^{MeOH} 256 (ε 24,280) and 284 mμ (ε 18,707), λ_{min}^{MeOH} 241 (ε 20,892) and 277 mμ (ε 18,511). The aryl ether linkage in compound III was removed by boiling with piperidine to give an excellent yield of 17β-acetoxy-2,4-dimethoxyestra-1,3,5(10)-trien-3-ol (IV), mp 174–175°, $[\alpha]^{27}D$ +44° ($CHCl_3$), λ_{max}^{MeOH} 272 mμ (ε 1020). Compound IV when allowed to react with methyl sulfate and anhydrous potassium carbonate in boiling acetone gave 17β-acetoxy-2,3,4-trimethoxyestra-1,3,5(10)-triene (V), mp 113–114°, $[\alpha]^{27}D$ +38° ($CHCl_3$), λ_{max}^{MeOH} 281 mμ (ε 1782). Alkaline hydrolysis of V with 1 *N* methanolic potassium hydroxide gave 2,3,4-trimethoxyestra-1,3,5(10)-trien-17β-ol (VI), mp 52–55° (crystallized from dilute methanol), $[\alpha]^{27}D$ +74° ($CHCl_3$), λ_{max}^{MeOH} 280 mμ (ε 1857). Compound VI exists in two dimorphic forms;[7] when crystallized from ether–petroleum ether (bp 30–60°) it melts at 131.5–132.5°.

In a second method for the synthesis of compound VI, 17β-acetoxy-2-methoxyestra-1,3,5(10)-trien-3-ol (VII)[4] was allowed to react with 1 equiv of concentrated nitric acid in acetic acid solution to give in good yield 17β-acetoxy-2-methoxy-4-nitroestra-1,3,5(10)-trien-3-ol (VIII), mp 204–207°, $[\alpha]^{27}D$ +196.5° ($CHCl_3$), λ_{max}^{MeOH} 276 mμ (ε 3536). The nitro compound VIII was allowed to react with an excess of diazomethane to give, in excellent yield, 17β-acetoxy-2,3-dimethoxy-4-nitroestra-1,3,5(10)-triene (IX), mp 212–214°, $[\alpha]^{27}D$ +102° ($CHCl_3$), λ_{max}^{MeOH} 274 mμ (ε 720). Catalytic hydrogenation of IX using Raney nickel catalyst gave 17β-acetoxy-4-amino-2,3-dimethoxeystra-1,3,5(10)-triene (X) in 85% yield; mp 176–178°, $[\alpha]^{27}D$ +47° ($CHCl_3$), λ_{max}^{MeOH} 282 mμ (ε 1285).

The amino compound X was diazotized with sodium nitrite in a solution of acetic acid–dioxane (1:1) and the diazo compound was decomposed by allowing the solution to stand at room temperature for 24 hr. The crude phenolic compound resulting from this reaction was methylated with methyl sulfate and anhydrous potassium carbonate in boiling acetone solution. Chromatographic purification of the reaction product gave in low yield 17β-acetoxy-2,3,4-trimethoxyestra-1,3,5(10)-triene (V), mp 114–115°, $[\alpha]^{26}D$ +34° ($CHCl_3$), λ_{max}^{MeOH} 281 mμ (ε 1778), identical in all respects with the one prepared by the first method.

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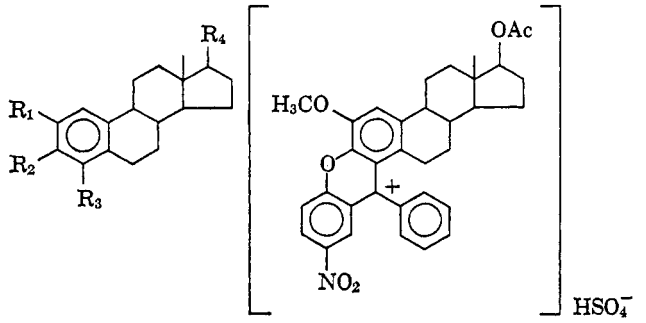
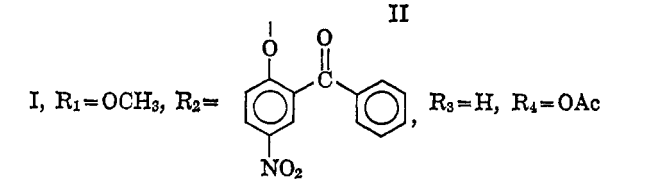
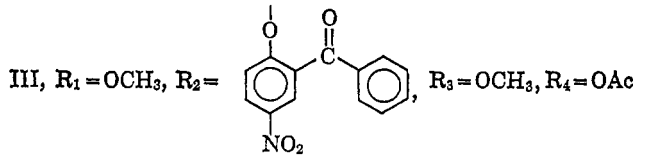


II





IV, $R_1 = OCH_3$, $R_2 = OH$, $R_3 = OCH_3$, $R_4 = OAc$
V, $R_1 = R_2 = R_3 = OCH_3$, $R_4 = OAc$
VI, $R_1 = R_2 = R_3 = OCH_3$, $R_4 = OH$
VII, $R_1 = OCH_3$, $R_2 = OH$, $R_3 = H$, $R_4 = OAc$
VIII, $R_1 = OCH_3$, $R_2 = OH$, $R_3 = NO_2$, $R_4 = OAc$
IX, $R_1 = R_2 = OCH_3$, $R_3 = NO_2$, $R_4 = OAc$
X, $R_1 = R_2 = OCH_3$, $R_3 = NH_2$, $R_4 = OAc$

(2) E. Allen and E. A. Doisy, *J. Am. Med. Assoc.*, **81**, 819 (1923).
(3) A full report on the pharmacology and biochemistry appears in L. R. Axelrod and D. H. Baeder, *Proc. Soc. Exptl. Biol. Med.*, in press.
(4) J. Fishman, *J. Am. Chem. Soc.*, **80**, 1213 (1958).
(5) J. D. Lowdon and J. A. Scott, *J. Chem. Soc.*, 269 (1953).
(6) All new compounds gave satisfactory analyses and were supported by infrared spectral data.
(7) The second polymorphic form was isolated by Dr. G. Brooke Hoey, Mallinckrodt Pharmaceuticals. The chemical identity of the two crystalline forms was authenticated by comparing their infrared spectra in carbon tetrachloride solution and by thin layer chromatography.

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