of $-NO_2$ to $-NHOH$ when charged to 99 p.s.i. The bomb was rocked for one hour, and reduction was shown to be complete by the absence of any internal pressure when the bomb was opened. The catalyst was removed by filtration, and removal of the solvent *in vacuo* at or below room temperature yielded a copious crystalline residue of N-2-pyridylhydroxylamine which reduced Tollens reagent immediately. This material was used in the next step without purification.

Ammonium Salt of N-2-Pyridyl-N-nitrosohydroxylamine.—The above residue was taken up in 200 ml. of ether and cooled to −5°. Gaseous ammonia was bubbled into the solution for several minutes, and then ethyl nitrite (prepared by the action of 1:1 HCl on 50 g. of $NaNO_2$ in 80 ml. of 95% ethanol) was concurrently introduced. The solution soon turned a very dark brown, and after a few minutes a cream-white precipitate appeared. This was filtered off and dried in a stream of ammonia. Further treatment of the filtrate with ammonia yielded additional product, which was again removed. Finally the solution was resaturated with ammonia and left in the refrigerator overnight. The following day additional product was removed; this time lag in precipitation has been noted with several Cupferron derivatives whose preparation will be reported later. The combined yield was 9.8 g. (78% over-all from 2-nitropyridine). Recrystallized from ethanol (soluble) and ether (insoluble), the material had a melting point of 133–135° dec.

Anal. Calcd. for $C_5H_8O_2N_4$: C, 38.46; H, 5.17; N, 35.88. Found: C, 38.69; H, 5.32; N, 35.35.

Precipitation Tests.—The metallic salts were employed in the form of sulfates (Al^{+++}, Fe^{++}), chlorides (Sn^{++}, Mn^{++}), nitrates (Bi^{+++}, Ag^{+}, Ni^{++}) and acetates (all the rest). One milliliter of a stock solution 0.02 *M* in metallic ion was treated with 4 ml. of 0.01 *M* chelating agent (water was used to dissolve the Pyridine Cupferron and 50% ethanol to dissolve the 7-indiazolol). Only those mixtures which gave precipitates within five minutes were graded as positive. It was noted that several mixtures gave precipitates after standing for 12 or even 48 hours.

Toxicity Tests.[10]—The toxicity of these substances toward *A. niger* was determined by means of the standard P.D.C. Agar Plate Test.[11]

(10) We are happy to acknowledge the assistance of Dr. S. S. Block, of our Chemical Engineering Staff, in obtaining the fungitoxicity data.

(11) Prevention of Deterioration Center, National Research Council, Dec., 1948.

DEPARTMENT OF CHEMISTRY AND DEPARTMENT OF CHEMICAL ENGINEERING
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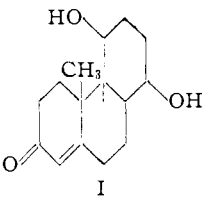
Some Optically Active Dodecahydrophenanthrenes[1]

BY R. M. LUKES AND L. H. SARETT

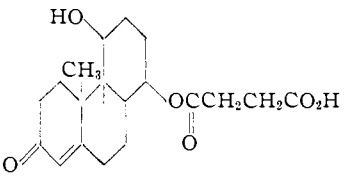
RECEIVED OCTOBER 14, 1953

During the course of our total synthesis of cortisone,[2] the possibility of optical resolution was investigated at various intermediate stages. One compound which proved to be readily separable into optical antipodes was the tricyclic dihydroxyketone I.[3] The 1-monohemisuccinate (II) afforded a brucine salt which after two crystallizations had a constant rotation. Alkaline hydrolysis of this salt gave an over-all yield of 45% of the theoretical amount of (−)-I.

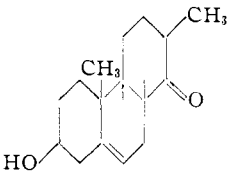
Some of the transformations that have been described in detail for racemic I[3] were applied to (−)-I with the idea of investigating some of the relationships of optical rotation to structure in this series. The products obtained are listed in Tables I and II.



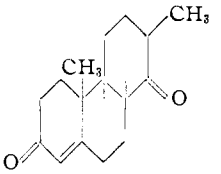
I



II



III



IV

The shift in molecular rotation (hereafter referred to as ΔM_D) for the conversion of a Δ^5-3β-hydroxysteroid to a Δ^4-3-ketosteroid has been found to be approximately +511°.[4] That perhydrophenanthrenes such as are described in this paper would be expected to show a comparable positive ΔM_D for the same transformation is demonstrated by the oxidation of the Köster–Logemann ketone III to the dione IV with its attendant ΔM_D of +472°.[5] Similarly, the hydrolysis of the Δ^5-3-ethylenedioxy derivatives of cholestenone,[6] 11-ketoprogesterone[7] and cortisone[8] to the parent Δ^4-3-ketosteroids results in positive ΔM_D values of +562°, +565° and +454°, respectively. However, when the *anti–trans* compounds (3) and (4) in Table II are converted to compounds (6) and (5) in Table I, respectively, *negative* ΔM_D values of −670° and −892° are obtained.[9] Thus it is evident that the tricyclic series presented in this paper is enantiomorphic to the steroids.

If one goes on and compares the ΔM_D values for the large variety of interconversions possible among the compounds in Tables I and II, it becomes immediately evident that there is a remarkable lack of consistency, and that the ΔM_D values are not predictable, and difficult to rationalize. The inevitable conclusion is that large and seemingly irregular vicinal effects, not unexpected in a series of three, four or five contiguous asymmetric centers, influence the rotatory contributions of those centers to such an extent as to make the

(1) Paper IX in the series "Approaches to the Total Synthesis of Adrenal Steroids."

(2) L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns and J. M. Constantin, THIS JOURNAL, **74**, 4974 (1952).

(3) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(4) D. H. R. Barton and W. Klyne, *Chemistry and Industry*, **67**, 755 (1948).

(5) H. Köster and W. Logemann, *Ber.*, **73**, 298 (1940).

(6) E. Fernholz and H. E. Stavely, Abstracts, 102nd Meeting of the Am. Chem. Soc., Atlantic City, N. J., 39M (1941).

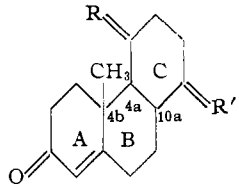
(7) J. M. Constantin, A. C. Haven, Jr., and L. H. Sarett, THIS JOURNAL, **75**, 1716 (1953).

(8) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

(9) The comparison is restricted to those pairs having the *anti-trans* configuration of C-4b, C-4a, and C-10a.

TABLE I

OPTICALLY ACTIVE DODECAHYDROPHENANTHRENES

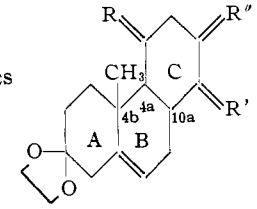


	R	R'	Configuration of C-4b, C-4a, C-10a	Cryst. solvent	M.p., °C.[a]	$[M]^{25}D$[b]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	HO, H	OH, H	*Anti-cis*	Methanol	225	−562°	71.97	72.18	8.86	8.74
2	O=	OH, H	*Anti-cis*	Benzene	171	−161°	72.55	72.25	8.12	8.07
3	O=	OAc, H	*Anti-cis*	Ether–methanol	107	−200°	70.32	70.17	7.64	7.71
4	O=	=O	*Anti-cis*	Acetone	154–157	−426°	73.15	73.27	7.37	7.61
5	O=	=O	*Anti-trans*	Ether	124	− 22°	73.15	73.05	7.37	7.14
6	HO, H	=O	*Anti-trans*	Ether	162	−404°	72.55	72.79	8.12	7.90
7	O=	OH, H	*Syn-trans*	Ether	145–150	−793°	72.55	72.26	8.12	8.26

[a] Melting points determined on a Kofler micro hotstage. [b] All rotations in chloroform, *c* 1.

TABLE II

OPTICALLY ACTIVE DODECAHYDROPHENANTHRENES



	R	R'	R"	Configuration of C-4b, C-4a, C-10a	Cryst. solvent	M.p.,[a] °C.	$[M]^{25}D$[b]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	HO, H	OH, H	H, H	*Anti-cis*	Ether	156	−456°	69.35	69.19	8.90	8.87
2	O=	=O	H, H	*Anti-cis*	Acetone	170–195	− 6°	...	...	..	..
3	HO, H	=O	H, H	*Anti-trans*	Ether	166	+266°	69.83	70.03	8.27	8.45
4	O=	=O	H, H	*Anti-trans*	Ether	109	+870°	70.32	70.24	7.64	7.85
5	O=	OH, H	H, H	*Anti-cis*	Ethyl acetate	157	−467°	69.83	70.06	8.27	8.13
6	O=	OH, H	H, H	*Syn-trans*	Ether	139	−467°	69.83	69.64	8.27	8.25
7	O=	=O	H, CO_2CH_3	*Anti-trans*	Ether	164	+654°	65.50	65.77	6.94	6.89
8	O=	=O	CH_3, CO_2CH_3	*Anti-trans*	Ether	149	+977°	66.28	66.58	7.23	6.99
9	O=	=O	CO_2CH_3, CH_3	*Anti-trans*	Petroleum ether	98–106	+937°	66.28	66.04	7.23	7.41

[a] Melting points determined on a Kofler micro hotstage. [b] All rotations in chloroform, *c* 1.

determination of the magnitude of the contribution of an individual asymmetric center impossible.

Experimental

4b-Methyl-1,2,3,4,4aα,4b,5,6,7,9,10,10a-dodecahydrophenanthrene-1β,4β-diol-7-one 1-Hemisuccinate (II).—A mixture of 90 g. of the dihydroxyketone I, 125 g. of succinic anhydride and 500 ml. of pyridine was heated at 100° for two hours. Then most of the pyridine was distilled *in vacuo*, and the residue was taken up in one liter of water. This solution was acidified with concentrated hydrochloric acid and was extracted twice with chloroform; the combined extracts were evaporated to 120 g. of crude crystalline residue. Recrystallization from methanol afforded 95 g. (76%) of II, m.p. 180°. Another crystalline form, m.p. 144–146°,

could be obtained by careful recrystallization from acetone–petroleum ether.

Anal. Calcd. for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.10; H, 7.66.

Resolution of the Hemisuccinate II and Recovery of (−)-I.—A dry mixture of 430 g. of the hemisuccinate II and 490 g. of anhydrous brucine alkaloid was dissolved in 9.5 l. of boiling acetone, and the solution was allowed to cool. Crystals began to deposit, and after 4 hours the supernatant liquor was decanted, evaporated to 1/2 volume, and placed in the refrigerator overnight to effect the precipitation of a second crop. The combined weight of the two crops was 415 g. (90%, $[\alpha]^{25}D$ −94 ± 2° (*c* 1, methanol)). Recrystallization from ethanol gave 392 g. (85%) of the brucine salt of (−)-I hemisuccinate, m.p. 145–152°, $[\alpha]^{25}D$ −102 ± 2° (*c* 1, methanol). Further recrystallization did not affect the rotation. The brucine salt (392 g.) was added to 1000 ml. of 1.5 *M* potassium carbonate solution, and the liberated brucine was extracted with chloroform. The aqueous solution was heated at 100° for 2.5 hours, cooled to 0°, and the crystals which formed were collected on a filter (106 g.). The filtrate was then extracted continuously for 2 days with chloroform. Evaporation of the chloroform extract left 20 g. of crystalline residue. The combined crystals were recrystallized from methanol, yielding 116 g. (70%) of (−)-I, m.p. 225°, $[\alpha]^{25}D$ −225 ± 2° (*c* 1, chloroform). Further recrystallization did not affect either the melting point or the rotation.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.18; H, 8.74.

The remainder of the compounds appearing in Tables I and II were prepared from (−)-I by previously published procedures.[3]

RESEARCH LABORATORIES OF MERCK & CO., INC.
RAHWAY, N. J.

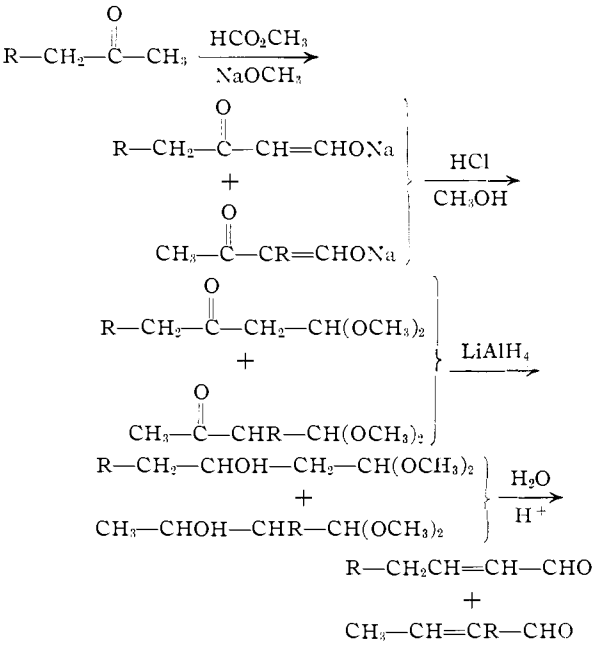
Hydroxymethylene Ketones. II. Orientation in the Condensation of Methyl Ethyl and Methyl *n*-Propyl Ketones with Methyl Formate

BY E. EARL ROYALS AND KENT C. BRANNOCK[1]

RECEIVED SEPTEMBER 28, 1953

The work of Benary[2] indicated that the condensation of methyl ethyl ketone with ethyl formate occurs at both the methyl and methylene units of the ketone. At the same time Benary detected only one isomer from the condensation of methyl *n*-propyl ketone with ethyl formate. Tracy and Elderfield,[3] and Joshi, Kaushal and Deshapande[4] detected only the methylene condensation product in the methyl ethyl ketone–ethyl formate reaction; however, in both cases multistep reaction sequences were used in which a minor isomer could easily be lost. While it is true that the predominant isomer from the methyl ethyl ketone–formic ester reaction is the methylene condensation product, and that from methyl *n*-propyl ketone is the methyl condensation product, the present work shows that appreciable amounts of the other isomers are formed under the usual reaction conditions.

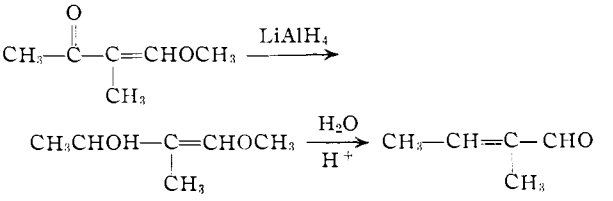
In the first paper of this series[5] the preparation of β-ketodimethyl acetals from hydroxymethylene ketones was described. Based on distillation data of their β-ketoacetals it was concluded that both hydroxymethylenemethyl ethyl ketone and hydroxymethylene-*n*-propylmethyl ketone consisted of mixtures of isomers arising from condensation of the ketones with methyl formate at their methyl and methylene groups. This conclusion has now been confirmed chemically by the reaction sequence



The yields of α,β-unsaturated aldehydes obtained from this reaction sequence are excellent, and the procedure is being investigated in this Laboratory as a synthetic method of wide applicability for this type of compound.

Although a quantitative separation of the α,β-unsaturated aldehydes in each case was impossible, we estimate that under our experimental conditions condensation of methyl ethyl ketone with methyl formate occurred to the extent of *ca.* 20–26% at the methyl group and *ca.* 74–80% at the methylene group while with methyl *n*-propyl ketone condensation was *ca.* 25–33% methylene and 67–75% methyl.

By a similar procedure the methoxymethylene-ethyl methyl ketone obtained previously[5] was shown to be derived from the methylene condensation product of methyl ethyl ketone and methyl formate.[6]



Experimental

The boiling points reported are uncorrected. Melting points (unless otherwise specified) were determined on a calibrated Fisher–Johns melting point apparatus.

β-Ketoacetal from Methyl Ethyl Ketone.—The crude β-ketodimethylacetal from methyl ethyl ketone,[5] 73 g. (0.5

(1) National Science Foundation Fellow, 1953–1954.

(2) Erich Benary, *Ber.*, **59**, 2198 (1926).

(3) A. H. Tracy and R. C. Elderfield, *J. Org. Chem.*, **6**, 63 (1941).

(4) S. N. Joshi, R. Kaushal and S. S. Deshapande, *J. Indian Chem. Soc.*, **18**, 479 (1941).

(5) E. E. Royals and K. C. Brannock, THIS JOURNAL, **75**, 2050 (1953).

(6) P. Seifert and H. Schinz, *Helv. Chim. Acta*, **34**, 728 (1951), have reported a similar sequence in the cyclic series which gave excellent yields of the α,β-unsaturated aldehydes.