TABLE I

PREPARATION OF *n*-BUTYLLITHIUM

Run	Time of addition, min.	Temp. during addition, °C.	Type of lithium	G. atoms lithium	Moles *n*-butyl bromide	Final concn., molar	Yield[a] %	Stirring after addition Hr.	Stirring after addition Temp., °C.
1	30	−20	Cut[b]	2.2	1.0	0.835	77.7	1.25	0–20
2	25	− 5	Cut	1.0	0.5	1.20	82.9	1	0
3	35	0	Sand[c]	1.0	0.5	1.47	77.3	2	0
4	35	−10	Cut	1.14	0.5	1.25	85.4[d]	2	0
5	35	−10	Wire	1.23	0.5	1.14	83.7[e]	2	0
6	15	−10	Cut	3.3	1.5	0.89	80.0	3	4

[a] Yield after filtration as determined by double-titration. [b] Prepared as described in THIS JOURNAL, **63**, 2327 (1940). [c] Supplied by the Metalloy Corp., Minneapolis, Minn. [d] In this run helium was used in place of nitrogen and double-titrations were made five minutes, one hour, and two hours after addition; yields were 78.5, 83.9, and 85.4%, respectively. [e] Yield determined by double-titration before filtration was 90%; the above yield was determined after storing sixteen hours at 10° following filtration.

mined by double-titration[1] was 90% before filtration and 83.7% after filtering and storing sixteen hours at 10°. After four days at 10°, the yield was 82.5%.

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Fluorene Analog of Amidone

BY DAVID GINSBURG[1] AND MANUEL M. BAIZER

Present interest in amidone analogs and derivatives[2,3] prompts us to report on the synthesis of a fluorene analog of amidone. This work was completed about a year ago but we have had no opportunity to establish the structure[4] of the isomer which was characterized.

Blicke and Zambito[5] state that the related "1,1-biphenylene-1-(β-dimethylaminoethyl)-butanone-2" is in the process of preparation. No details have appeared to date.

Experimental[6]

9-Formylfluorene.—This compound was prepared in 74% yield by the procedure of Von and Wagner.[7]

9-Formylfluorene Oxime.—A 78% yield was obtained by the procedure of Vorländer.[8]

9-Cyanofluorene.—A 90% yield was obtained in the dehydration of 9-formylfluorene oxime by thionyl chloride in absolute ether.[8]

Condensation of 9-Cyanofluorene with 1-Dimethylamino-2-chloropropane.—The procedure followed was similar to the one used in the condensation of diphenylacetonitrile with the chloroamine to yield the precursors of the amidones.[9]

In a 250-ml., three-necked flask, equipped with thermometer, mercury-sealed stirrer and reflux condenser, 19.1 g. (0.1 mole) of 9-cyanofluorene and 12.2 g. (0.1 mole) of 1-dimethylamino-2-chloropropane were dissolved in 100 ml. of dry benzene at 25°. Sodium amide (4.3 g., 0.11 mole) was added, portionwise, with continuous stirring in the course of thirty minutes. The temperature rose spontaneously to 40° in one hour; ammonia was evolved. The mixture was refluxed for thirty minutes, cooled and 50 ml. of water added. The benzene layer was separated and shaken with 50 ml. of 20% hydrochloric acid. The benzene layer on evaporation left 2.5 g. of unchanged 9-cyanofluorene. The acid extract was made alkaline by the addition of 33% sodium hydroxide, and the oil which separated was extracted with 200 ml. of ether. The ethereal solution was dried and the solvent removed by distillation. The residual oil, presumed by analogy to be mixture (I) of 9-cyano-9-(β-dimethylaminopropyl)-fluorene and 9-cyano-9-(α-methyl-β-dimethylaminoethyl)-fluorene, weighed 25.5 g. Upon distillation a yellow oil was obtained; b. p. 195–199° (8 mm.).

Reaction of I with Ethylmagnesium Bromide.—A Grignard reagent was prepared from 9.7 g. (0.40 mole) of magnesium turnings and 44 g. (0.38 mole) of ethyl bromide in 100 ml. of dry ether. To the ethereal solution was added, in one portion, a solution of 29 g. (0.11 mole) of I in 35 ml. of dry xylene. A greenish precipitate formed after a few minutes of heating under reflux in an oil-bath at 95–100°. The heating was continued for three and one-half hours; the mixture was then decomposed, while still hot, by the careful addition of 40 ml. of concentrated hydrochloric acid dissolved in 100 ml. of water. After the addition of benzene three layers were formed. The two upper layers were removed together and heated on a steam-bath until the solvents had been vaporized. The residual oily hydrobromide was moistened with alcohol and chilled briefly in an acetone–solid carbon dioxide-bath, whereupon crystallization occurred. The solid was filtered and recrystallized from ethanol. The yield of II,[10] m. p. 232–234°, was about 75% based upon one-half the input of I.

Anal. Calcd. for $C_{21}H_{26}BrNO$: C, 64.94; H, 6.75; N, 3.61. Found: C, 64.43; H, 7.02; N, 3.77.[11]

The melting point of the base, liberated from II, is 57–60° and of the hydrochloride 262–263°.

(1) Present address: Daniel Sieff Research Institute, Rehovoth, Israel.

(2) Gardner, *et al.*, THIS JOURNAL, **70**, 2906 (1948).

(3) May and Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

(4) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 2454 (1947), outline a structure proof for the isomeric nitriles which are the precursors of the amidones.

(5) Abstracts of American Chemical Society meeting April, 1947, p. 3K.

(6) Melting points and boiling points are not corrected.

(7) Von and Wagner, *J. Org. Chem.*, **9**, 162 (1944).

(8) Vorländer, *Ber.*, **44**, 2468 (1911).

(9) O. P. B. Report PB 981, p. 97.

(10) By analogy with the findings in the amidone synthesis,[9] we consider it probable that II is 9-propionyl-9-(β-dimethylaminopropyl)-fluorene hydrobromide and that the by-products remain in the mother liquors.

(11) Microanalyses by Schwarzkopf Laboratories, Elmhurst, L. I., N. Y.

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The Configuration at the 20-Position in Certain Steroids

BY W. KLYNE AND D. H. R. BARTON

Isomeric C_{21} steroids bearing a secondary hydroxyl group at C_{20} are commonly distinguished

by the indices α and β, without parentheses. Recently Fieser and Fieser[1] have discussed the relationships between the known configurations at C_{17} and these hitherto arbitrarily designated configurations at C_{20}. They have elucidated with a high degree of probability the stereochemistry at C_{20} of certain adrenal cortex steroids and related compounds having the side-chain in the 17(β) position and a hydroxyl in the 17(α) position. The convention used by Fieser and Fieser to designate C_{20} isomers, which has a definite stereochemical meaning, is so chosen as to agree with the arbitrary nomenclature of Reichstein.[2] Previously the latter author had pointed out that his use of the symbols 20α and 20β did not imply any agreement between his convention and that adopted by Marker[3] for C_{21} steroids having a hydrogen atom at C_{17}. Marker used the designation 20α for substances having the same configuration at C_{20} as the common pregnanediol of human pregnancy urine,[4] and 20β for the epimeric configuration.

The compounds whose C_{20} configurations were allotted by Fieser and Fieser on purely chemical grounds were 17(α),20 diols and 17(α),20,21-triols, and the arguments were supported by reference to molecular rotation data.[5] Fieser and Fieser showed that the Δ_1 values (changes in molecular rotation on acetylation)[6] of 20-hydroxyl compounds were characteristic, being in the 17-*n* series—strongly positive for their 20(β) compounds and negative for their 20(α) compounds. These authors then allotted configurations to certain 20,21 diols having a hydrogen atom in the 17(α)-position on the basis of rotation evidence. They made no reference to compounds previously covered by Marker's convention, since the literature contains no adequate data on the rotations of these substances.

We have recently determined the rotations of some simple 17(α)-H, 20–OH compounds and their acetates. The Δ_1 values of these compounds agree so well with the Δ_1 values of the corresponding 17(α)–OH, 20–OH compounds (Table I) that we feel certain that the molecular rotation difference method is valid in this case. The data show that the convention of Fieser and Fieser and that of Marker are in agreement. Marker's 20α and 20β compounds are, respectively, 20(α) and 20(β) on the Fieser convention.

(1) Fieser and Fieser, *Experientia*, **4**, 285 (1948).

(2) Prins and Reichstein, *Helv. Chim. Acta*, **23**, 1490 (1940); von Euw and Reichstein, *ibid.*, **24**, 401 (1941).

(3) Marker, Kamm, Wittle, Oakwood, Lawson and Laucius. THIS JOURNAL, **59**, 2291 (1937).

(4) Marrian, *Biochem. J.*, **23**, 1090 (1929).

(5) Previous work both among sugars and among steroids [*cf.* Barton and Cox, *J. Chem. Soc.*, 783 (1948)] has shown that molecular rotation differences are not always strictly additive when hydroxyl groups attached to neighboring carbon atoms are considered. However, qualitative agreement between data is sometimes sufficient to permit the use of the molecular rotation difference method in the assignment of configurations.

(6) These authors neglected the contributions of other positions (C_3 and/or C_{21}) to the Δ_1 values of their compounds. Since Δ_1 values for the 20(β) position are large, while those for the 3(β) and 21 positions are small, this procedure was justified.

TABLE I

Δ_1 VALUES AT C_{20} FOR 20-HYDROXY AND 17(α),20-DIHYDROXY REFERENCE COMPOUNDS IN THE 17-*n* SERIES

All rotations are for the Na_D line; solvents, Al = ethanol, An = acetone, Chf = chloroform, M = methanol

	[M]D 20-hydroxy	[M]D 20-acetate	Δ_1 Value (at C_{20})	Ref.
Compounds with 17(α)-H		C_{20} Configurations according to Marker[3]		
Allopregnanediol-3(β),20α	+72 Chf	+ 28[a] Chf	− 44	[b]
Allopregnanediol-3(β),-20β 3-acetate	−22 Chf	+ 89 Chf	+111	[b]
Compounds with 17(α)-OH		C_{20} configurations according to Fieser and Fieser		
Allopregnanetriol-3(β),17(α),20(α) (Reichstein's O)	−44 M	− 85[a] An	− 41	[c]
Allopregnanetriol-3(β),17(α),20(β) (Reichstein's J)	−27 Al	+124[a] An	+151	[c]

[a] Calculated from the values for the 3:20 diacetates by subtracting the Δ_1 value for the 3(β) position (−29); see Barton, *J. Chem. Soc.*, 1116 (1946). [b] This paper. [c] Steiger and Reichstein, *Helv. Chim. Acta*, 21, 546 (1938).

The Δ_1 values (at C_{20}) for the more highly-substituted 17-*n* compounds do not, as a rule, agree quantitatively with the values in Table I. They do, however, fall clearly into two groups, *viz.*,

TABLE II

Δ_1 VALUES AT C_{20} FOR 17-*iso*-20-HYDROXY-STEROIDS

Indices "α," "β" allotted by Fieser and Fieser[1]

Compound	Δ_1 Value (at C_{20})[a]		Ref.
17-Iso-5-allopregnanetriol-3(β),17(β),20"α"	+ 13		*b*
17-Iso-5-allopregnanetriol-3(β),17(β),20"β"		+ 17	*c*
17-Iso-Δ^5-pregnenetriol-3(β),17(β),20"β"		+ 60	*d*
17-Iso-5-allopregnanetriol-3(β),17(β),20"α",21	−109		*e, f, g*
17-Iso-5-allopregnanetriol-3(β),17(β),20"β",21		+ 44	*e, f*
17-Iso-Δ^5-pregnenetetrol-3(β),17(β),20"α",21	−116		*h*
17-Iso-Δ^4-pregnenetriol-17(β),20"β",21-3-one		− 25	*h*
Standard value for 20(α)-hydroxy-17-*n*-compound	− 44		*i*
Standard value for 20(β)-hydroxy-17-*n*-compound		+111	*i*

[a] Calculated from the total Δ_1 values by subtraction of the Δ_1 values for the 3 and/or 21 positions, *cf.* Barton, *J. Chem. Soc.*, 1116 (1946); Barton and Klyne, *Chem. and Ind.*, 755 (1948). [b] Prins and Reichstein, *Helv. Chim. Acta*, **23**, 1490 (1940). [c] Reich, Sutter and Reichstein, *ibid.*, **23**, 170 (1940). [d] Butenandt, Schmidt-Thomé and Paul, *Ber.*, **72**, 1112 (1939). [e] Serini, Logemann and Hildebrand, *ibid.*, **72**, 391 (1939). [f] Reich, Montigel and Reichstein, *Helv. Chim. Acta*, 24, 977 (1941). [g] Prins and Reichstein, *ibid.*, **25**, 300 (1942). [h] Serini and Logemann, *Ber.*, 71, 1362 (1938). [i] This paper.

small negative values for 20(α) compounds (*e. g.*, pregnanediol-20(α), 21-dione-3,11, $\Delta_1 = -29$) and large positive values for 20(β) compounds (*e. g.*, Reichstein's compounds K, E and U, which are all (17(α),20(β),21 triols, $\Delta_1 = +306, +428, +308$, respectively). The Δ_1 value (at C_{20}) of the pregnanediol-3(α),20-one-11 3-acetate of Sarett[7] (+91) shows that it is a 20(β) compound, as might be expected from its method of preparation.

Table II shows the Δ_1 values (at C_{20}) for 17(β), 20 diols of the 17-*iso* series. It will be seen that there is no really convincing agreement with the standard Δ_1 values in the 17-*n* series. Since, also, in the comparable case of hydroxyl groups at C_{11} and C_{12} the molecular rotation data are in disagreement with the accepted configurations,[8,9] we feel that the conclusions of Fieser and Fieser regarding the 17-*iso* compounds, although possibly correct, should at present be treated with some reserve.

We are indebted to N. V. Organon, Oss, Holland, for a generous gift of pregnenolone acetate.

Experimental[10]

Allopregnanediol-3(β),20(α) Diacetate.—Allopregnanol-3(β)-one-20 acetate was reduced with sodium and boiling ethanol.[11] The product was acetylated and the acetates chromatographed on alumina. Allopregnanediol-3(β),20(α)-diacetate after repeated crystallization from light petroleum had m.p. 163–165° (reported,[11] 165–168°); $[\alpha]_D$ −0.3° (*c*, 3.3), $[M]_D$ −1°.

Allopregnanediol-3(β),20(α).—The diacetate was hydrolyzed by boiling for two hours with aqueous alcoholic potassium hydroxide. The diol, recrystallized once from ether and once from acetone, had m.p. 218–219° (reported[11] 220–222°) $[\alpha]_D$ +23° (*c*, 0.9), $[M]_D$ + 72°.

Allopregnanediol-3(β),20(β) 3-Acetate.—Δ^5-Pregnenol-3(β)-one-20 acetate was hydrogenated in ether-acetic acid solution using a platinum catalyst until the uptake of hydrogen was complete. The product was recrystallized repeatedly from methanol to give allopregnanediol-3(β),20(β) 3-acetate, m. p. 168–169°, $[\alpha]_D$ −6° (*c*, 3.6), $[M]_D$ −22° (1-dm. macro-tube).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.2; H, 10.6. Found: C, 76.5; H, 10.5.

Allopregnanediol-3(β),20(β)-diacetate.—The monoacetate was refluxed with acetic anhydride for one hour. The product was chromatographed on alumina and recrystallized from methanol to give the diacetate, m. p. 141–142° (reported[12] 142–143°), $[\alpha]_D$ +22° (c, 5.2), $[M]_D$ +89°.

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(7) Sarett, THIS JOURNAL, **70**, 1690 (1948). By arguments similar to those of Fieser and Fieser, based on the method of formation, Sarett's pregnanetriol-3(α),17,20-one-11 (diacetate m. p. 227–228°) must be 17(α),20(β), and his pregnanetriol-17(α),20,21-dione-3,11 (diacetate, m. p. 212–213°) must be 20(β).

(8) Gallagher, *J. Biol. Chem.*, **162**, 539 (1946).

(9) Wintersteiner, Moore and Reinhardt, *ibid.*, **162**, 707 (1946).

(10) All rotations were determined in $CHCl_3$ solution for the Na_D line at 20–25°. A 0.5 dm. micro-tube was used unless stated to the contrary.

(11) Meystre and Miescher, *Helv. Chim. Acta*, **29**, 33 (1946).

(12) Marker, Kamm, Jones and Oakwood, THIS JOURNAL, **59**, 614 (1937).

Studies in *p*-Cymene. II.[1] The Isomeric Aldehydes Derived from *p*-Cymene

BY CHARLES T. LESTER, RAYMOND E. DONALDSON AND JAMES C. OSWALD[2]

We have prepared the isomeric aldehydes, 2-methyl-5-isopropylbenzaldehyde[3] and 3-methyl-6-isopropylbenzaldehyde,[4] and studied their behavior when subjected to a variety of aldehyde reactions. Our objective was not to realize maximum yields, but to observe what differences, if any, were shown in the reactivities of the isomeric compounds.

Without exception all the experiments reported below indicate that the aldehyde group of 2-methyl-5-isopropylbenzaldehyde is more reactive than the aldehyde group of 3-methyl-6-isopropylbenzaldehyde. This difference is most noticeable in the self-condensation Cannizzaro reaction. The difference in reactivity of the isomeric aldehydes is in agreement with our previous report[1] concerning the saponification rate of the isomeric esters derived from *p*-cymene.

Experimental[4a]

Preparation of 2-Methyl-5-isopropylbenzaldehyde.—*p*-Cymene was converted into 2-methyl-5-isopropylbenzyl chloride[5] in 49% yield. The aldehyde was prepared from the substituted benzyl chloride by the method of Sommelet.[6] This reaction was carried out with 37.5 g. of the chloride and 42 g. of hexamethylenetetramine. The aldehyde was isolated as the bisulfite addition compound; average yield, based on six preparations, 25 g., 65%. Hydrolysis of the bisulfite compound gave the aldehyde, b. p. 125° (20 mm.), in 65% yield. The aldehyde was converted, without modification of standard procedures, into a 2,4-dinitrophenylhydrazone,[7] m. p. 190–191°, and a semicarbazone,[8] m. p. 170–171°.

Preparation of 3-Methyl-6-isopropylbenzaldehyde.—The aldehyde was prepared from 3-bromo-*p*-cymene[9] according to the procedure of Smith and Nichols.[10] From the Grignard reagent prepared from 63.9 g. of 3-bromo-*p*-cymene was obtained (average of eight preparations) 21.6 g., 27% yield, of the aldehyde bisulfite compound. Hydrolysis of the bisulfite compound gave a 60% yield of the aldehyde, b. p. 123° (20 mm.). Attempts to prepare a 2,4-dinitrophenylhydrazone[7] and a semicarbazone[8] by the usual procedures were unsuccessful. However, when the aldehyde and proper reagents were heated in a boiling water-bath for one hour, a 2,4-dinitrophenylhydrazone, m. p. 192–193°, and a semicarbazone, m. p. 177–178° were obtained.

Reaction of the Aldehydes with Acetone.—The aldehydes were treated with the same molar quantities of reagents as described by Porter and Stewart[11] for benzaldehyde. Each reaction mixture was refluxed for five min-

(1) Lester and Bailey, THIS JOURNAL, **38**, 375 (1946).

(2) Present address: Georgia State Department of Agriculture, Atlanta, Georgia.

(3) Verley, *Bull. soc. chim.*, [3] **17**, 906 (1897).

(4) Blum-Bergmann, *J. Chem. Soc.*, **1**, 1930 (1935).

(4a) All melting points are uncorrected.

(5) Whittleston, THIS JOURNAL, **59**, 825 (1937).

(6) Sommelet, *Compt. rend.*, **157**, 852 (1913).

(7) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 143.

(8) Shriner and Fuson, *ibid.*, p. 142.

(9) Fileti and Crosa, *Gazz. chim. ital.*, **16**, 292 (1886).

(10) Smith and Nichols, *J. Org. Chem.*, **6**, 489 (1941).

(11) Porter and Stewart, "Organic Chemistry for the Laboratory," Ginn and Co., Boston, Mass., 1943, p. 103.