residue from hexane gave 0.83 g. of a white solid, melting at 142–144°. The substance was purified for analysis by dissolution in warm 5% sodium hydroxide, re-precipitation with acid, and finally recrystallization from hexane. The pure lactone (II) had m.p. 145–146° (shrinking at 135–140°).

Anal. Calc'd for $C_9H_{12}O_2$: C, 71.04; H, 7.95; Molecular weight, 152. Found: C, 71.02; H, 7.95; Molecular weight (in camphor), 147.

II was insoluble in bicarbonate or cold sodium hydroxide. It gave negative tests with 2,4-dinitrophenylhydrazine and potassium permanganate.

Reduction of II *to* I. A solution of 0.570 g. of II in 25 cc. of absolute ether was added to a slurry of 0.30 g. of lithium aluminum hydride in 50 cc. of ether with vigorous stirring. The mixture was heated at reflux for 3 hours and worked up with isopropyl alcohol (3.3 cc.) and saturated sodium chloride (3.3 cc.) as above. Evaporation of the solvents and recrystallization of the residue from benzene-hexane gave 0.450 g. of I, m.p. 59–61°, alone or mixed with an authentic sample.

Permanganate oxidation of I. A mixture of 1.0 g. of I, 2 cc. of 10% sodium hydroxide, and 100 g. of ice was stirred and treated with 135 cc. of 1% potassium permanganate. The mixture was allowed to stand overnight, the manganese dioxide was removed by filtration, and the filtrate was acidified with hydrochloric acid and extracted with chloroform. The extract was dried over magnesium sulfate, filtered, evaporated, the residue leached with 3 cc. of hot 5% sodium hydroxide and the insoluble gummy residue filtered off. The filtrate was acidified and the precipitated solid was washed with 5% sodium bicarbonate and then with water to give 0.11 g. of white solid, m.p. 139–141°. Since the m.p. of pure II is rather indefinite (*vide supra*), identity was established by comparison of the infrared spectra of chloroform solutions of II and the oxidation product. These were superimposable.

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Quinoxaline Studies. IX. The Preparation of 3-Methyl-6- and -7-bromo-2-quinoxalinols[1]

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Dawson, Newbold, and Spring[2] condensed 3,4-diaminochlorobenzene with pyruvic acid; this equivocal synthesis gave a mixture of 3-methyl-6- and -7-chloro-2-quinoxalinols, from which 3-methyl-7-chloro-2-quinoxalinol was isolated and identified. The authors of this paper wish to report the syntheses by unequivocal methods of both 3-methyl-6- and -7-bromo-2-quinoxalinols. Syntheses of the bromoquinoxalinols were studied because these compounds would be expected to lend themselves more readily to subsequent transformations involving the halo group than would the corresponding chloroquinoxalinols.

(1) Abstracted in part from the M.S. thesis of R. V. D., University of Miami, 1955.

(2) Dawson, Newbold, and Spring, *J. Chem. Soc.*, 2579 (1949).

Reaction of 2-nitro-4-bromoaniline with *dl*-α-bromopropionic acid gave less than 1% yield of the desired N-(2-nitro-4-bromophenyl)-*dl*-α-alanine. A second, more fruitful, method of preparing N-(2-nitro-4-bromophenyl)-*dl*-α-alanine was found to be the condensation of *dl*-α-alanine with 2,5-dibromonitrobenzene. Experimental results confirmed the expectation that the *ortho* halogen of the aromatic compound would react in this instance.

The reductive cyclization of N-(2-nitro-4-bromophenyl)-*dl*-α-alanine was carried out chemically with alcoholic hydrochloric acid and iron by the method of West,[3] with a suspension of ferrous hydroxide in ammonium hydroxide according to the procedure of Singer and Shive,[4] and, in best yield, catalytically over a Raney nickel catalyst at low hydrogen pressure. The probable intermediate, 3-methyl-3,4-dihydro-7-bromo-2-quinoxalinol, was not isolated, but was oxidized directly with basic hydrogen peroxide solution to the desired product, 3-methyl-7-bromo-2-quinoxalinol. Reductive cyclizations (followed by oxidation) over palladium and platinum catalysts resulted in hydrogenolysis of the bromo group, for only 3-methyl-2-quinoxalinol was obtained when these noble metal hydrogenation catalysts were used.

Condensation of 2,4-dibromonitrobenzene with *dl*-α-alanine gave the desired N-(2-nitro-5-bromophenyl)-*dl*-α-alanine. Ogata and Tsuchida[5] recently observed that in nucleophilic attack on *o,p*-dihalonitrobenzenes, the *ortho* halogen preferentially reacts with uncharged nucleophilic reagents such as ammonia and amines. This synthesis further confirms their observations.

The reductive cyclization of N-(2-nitro-5-bromophenyl)-*dl*-α-alanine (followed by oxidation) was successfully executed by both chemical and catalytic means to give 3-methyl-6-bromo-2-quinoxalinol.

EXPERIMENTAL PROCEDURES

N-(2-Nitro-4-bromophenyl)-dl-α-alanine. A mixture of 84.3 g. of 2,5-dibromonitrobenzene,[6] 26.7 g. of *dl*-α-alanine, 50.4 g. of sodium bicarbonate, 50 ml. of 95% ethanol, and 10 ml. of water was refluxed for 42 hours. The reaction mixture was evaporated to dryness on a steam-bath and was triturated with five 15-ml. portions of 10% sodium hydroxide solution, followed by one 25-ml. portion of water. After the triturate was filtered, it was brought to *p*H 4 with 20% hydrochloric acid to give 31.4 g. of a tan precipitate m.p. 145–155°. This material was recrystallized from benzene (24 ml./g.) 8 times, using charcoal and filter aid, to give 11.2 g. (13%) of yellow platelets m.p. 162–164°.

Anal. Calc'd for $C_9H_9BrN_2O_4$ (289.1): Br, 27.65; N, 9.69. Found: Br, 27.47; N, 9.61.

The neutral residue from the condensation gave 35.2 g. (41.8%) of 2,5-dibromonitrobenzene m.p. 81–85°; reported[6] for 2,5-dibromonitrobenzene m.p. 82–82.5°.

3-Methyl-7-bromo-2-quinoxalinol. In a Parr pressure flask

(3) West, *J. Chem. Soc.*, **127**, 494 (1925).

(4) Singer and Shive, *J. Org. Chem.*, **20**, 1458 (1955).

(5) Ogata and Tsuchida, *J. Org. Chem.*, **20**, 1631 (1955).

(6) Hammond and Modic, *J. Am. Chem. Soc.*, **75**, 1385 (1953).

were placed 5.8 g. of N-(2-nitro-4-bromophenyl)-*dl*-α-alanine, 50 ml. of 95% ethanol, and 5 g. of Raney nickel catalyst.[7] Hydrogen uptake ceased when about 75% of the theoretical quantity of hydrogen had been absorbed by the reaction mixture in 25 minutes at 25° and 60 p.s.i.

The reaction mixture was filtered, and the filtrate was evaporated to dryness on a steam-bath. To the residue were added 50 ml. of 10% sodium hydroxide solution and 15 ml. of 30% hydrogen peroxide. After being heated on the steam-bath for 1 hour, the mixture was filtered; the filtrate was brought to *p*H 4 with 20% hydrochloric acid to give 3.3 g. of tan powder m.p. 252–265°. Sublimation of the crude product at 195°/1 mm. gave 2.9 g. of yellow powder m.p. 273–280°. The sublimate was purified for analysis by 6 recrystallizations, using charcoal and filter aid, from 95% ethanol (100 ml./g.) to give 1.0 g. (21%) of white platelets m.p. 291–293° dec.

Absorption maxima, mμ, and molar absorptivity ($\epsilon \times 10^{+3}$), 95% ethanol: 232 (20.3); 282.5 (7.0); 327.5 (9.2); 338 (9.6); 0.1 *N* NaOH: 240 (29.8); 343.5 (11.1).

Dawson, *et al.*,[2] reported molar absorptivity in 0.1 *N* NaOH for 3-methyl-7-chloro-2-quinoxalinol to be 240 (27); 345 (9.1).

Anal. Calc'd for $C_9H_7BrN_2O$ (239.1): C, 45.21; H, 2.95; Br, 33.43; N, 11.72. Found: C, 45.32; H, 2.88; Br, 33.11; N, 11.60.

2,4-Dibromoacetanilide. This substance was prepared by a modification of Chattaway, Orton, and Hurtley's[8] procedure. In a 10 l. square battery jar equipped with a broad bladed stirrer were placed 84 g. of sodium bicarbonate, 1 l. of water, and 54 g. of acetanilide. While the mixture was violently stirred, 41 ml. of bromine was added dropwise over a 1 hour period at 25°. The light yellow precipitate of N,4-dibromoacetanilide was filtered, rinsed with water, then stirred with 300 ml. of boiling water for 1 hour. The crude 2,4-dibromoacetanilide was filtered from the cool mixture, rinsed, and again boiled in 300 ml. of water for 5 minutes. The product was filtered, rinsed, and dried to give 102.5 g. of tan powder m.p. 130–135°.

Two recrystallizations from 95% ethanol (3 ml./g.), using charcoal and filter aid, gave 78.2 g. (67%) of 2,4-dibromoacetanilide m.p. 145–147°. Reported[8,9] for this compound m.p. 146°.

The amide was hydrolyzed and steam-distilled, according to the direction of Chattaway and Clemo,[9] to give 2,4-dibromoaniline in 71% yield.

2,4-Dibromonitrobenzene. This material was prepared from *m*-dibromobenzene[10] using the same directions given by Hammond and Modic[6] for the nitration of *p*-dibromobenzene. The crude product, m.p. 55–59°, was recrystallized from 95% ethanol-ligroin (60–90°) (1:4; 2 ml./g.) in 74% yield, m.p. 61–62°. Reported[11] for 2,4-dibromonitrobenzene, m.p. 62°.

N-(2-nitro-5-bromophenyl)-dl-α-alanine. This material was prepared in 36% yield from 2,4-dibromonitrobenzene and *dl*-α-alanine using the same procedure given above for the preparation of N-(2-nitro-4-bromophenyl)-*dl*-α-alanine. The crude product, m.p. 165–170°, was recrystallized twice from benzene (20 ml./g.), using charcoal and filter aid, to give yellow needles m.p. 175–177°.

Anal. Calc'd for $C_9H_9BrN_2O_4$ (289.1): Br, 27.65; N, 9.69. Found: Br, 27.42; N, 9.66.

3-Methyl-6-bromo-2-quinoxalinol. This material was prepared in 11.4% yield from N-(2-nitro-5-bromophenyl)-*dl*-α-alanine, using the same procedure given above for the preparation of 3-methyl-7-bromo-2-quinoxalinol. The crude product, m.p. 200–220°, was sublimed (m.p. 205–230°), then recrystallized four times from 95% ethanol (10 ml./g.), using charcoal and filter aid, to give a felt-like mat of white needles, which melted at 252.5–254°, then solidified to a mass of interlacing prisms which melted again at 260–262° dec.

Absorption maxima, mμ, and molar absorptivity ($\epsilon \times 10^{+3}$), 95% ethanol: 240 (24.4); 275 (1.76); 347 (6.48); 0.1 *N* NaOH: 244 (25.8); 350 (8.25).

Anal. Calc'd for $C_9H_7BrN_2O$ (239.1): C, 45.21; H, 2.95; Br, 33.43; N, 11.72. Found: C, 45.28; H, 2.67; Br, 33.54; N, 11.81.

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(7) Mozingo, *Org. Syntheses*, **21**, 15 (1941).

(8) Chattaway, Orton, and Hurtley, *Ber.*, **32**, 3635 (1900).

(9) Chattaway and Clemo, *J. Chem. Soc.*, **109**, 89 (1916).

(10) Jackson and Cohoe, *Am. Chem. J.*, **26**, 3 (1901).

(11) Holleman, *Rec. trav. chim.*, **25**, 193 (1906).

3β-Hydroxypregn-4-en-20-one

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This compound was required for a series of biological studies. Its progestational activity is of the same order as progesterone.

3β-Hydroxypregn-5-en-20-one acetate was converted to its 20-ethylene ketal by treating with ethylene glycol in benzene solution with a catalytic amount of *p*-toluenesulfonic acid. This acetate was saponified with methanolic sodium hydroxide and the resulting free alcohol was oxidized with aluminum isopropoxide to progesterone-20-ethylene ketal.[1] The latter compound was reduced with sodium borohydride presumably to a mixture of 3α- and 3β-hydroxypregn-4-en-20-one-20-ethylene ketal. The pure 3β-isomer, obtained by digitonide separation, furnished the desired 3β-hydroxypregn-4-en-20-one on treatment with ethanolic oxalic acid[2] at room temperature.

EXPERIMENTAL[3]

3β-Hydroxypregn-5-en-20-one-20-ethylene ketal acetate. A solution of 15 g. of 3β-hydroxypregn-5-en-20-one acetate in 530 cc. of dry benzene and 16 cc. of ethylene glycol was refluxed with 1.0 g. of *p*-toluenesulfonic acid employing a water separator. After 18 hours, the separation of water was complete and the mixture was washed with a saturated aqueous bicarbonate solution, dried over sodium sulfate,

(1) K. Junkmann, *Arch. exptl. Pathol. Pharmakol.*, **223**, 244 (1954).

(2) In view of the facile elimination of the allylic hydroxyl only very mild acidic conditions can be used. Compare H.-W. Wanzlick, G. Gollmer, and H. Milz, *Ber.*, **88**, 69 (1955).

(3) All melting points are uncorrected. Microanalyses are by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y., IR absorption spectra by Mr. Paul Skogstrom. The rotations are for chloroform solutions and were determined in a 1-dm. tube at wave length 5893 A. (D). "Woelm," non-alkaline aluminum oxide, activity grade 1 was used for chromatography.