into the relationship of structure and antimalarial activity of the acridines.[3]

The following conclusions can be drawn on the basis of duckling tests[4] on the compounds reported here: (a) A substituent in the 1 position (Fig. 1) appears to be mildly dystherapeutic:

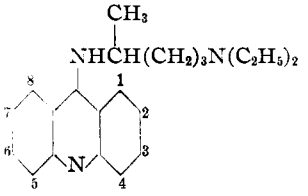

Fig. 1.

(b) One substituent in the 4 or 5 position gives a regular dystherapeutic effect. Since completion of this work, these findings have been supported by Hall and Turner[5] with the amendment that upon substitution in both the 4 and 5 positions, increased activity may be expected.

Experimental

The *o*-chloro-, *o*-bromo and 2,4-dichlorobenzoic acids were obtained commercially. The *o*-chlorobenzoic acid was purified[6] before use.

The anilines with the exception of 2-chloro-4-methoxy and 3,5-dichloroaniline were commercial samples which were distilled or crystallized.

3,5-Dichloroaniline was prepared from 2,6-dichloro-4-nitroaniline by deamination and reduction of the resulting 3,5-dichloronitrobenzene.[7]

2-Chloro-4-methoxyaniline was prepared quite readily in large quantities from technical *p*-anisidine.[8] Phosgene passed into an aqueous solution of pyridine and technical *p*-anisidine gave an 82% yield of N,N'-di-(*p*-methoxy)-phenylurea which was dried and chlorinated in *sym*-tetrachloroethane to give a quantitative yield of the dichlorinated urea. Treatment with 28% ammonium hydroxide at 150–160° for five hours gave a 90–95% yield of 2-chloro-4-methoxyaniline, b. p. 141–144° (25 mm.); N-acetyl derivative, m. p. 113–114.5° (lit.,[8] m. p. 114°).

Diphenylamine-2-carboxylic Acids.—The diphenylaminecarboxylic acids were prepared according to the method of Ullmann.[9] The following more detailed description is typical of the method used for the preparation.

5-Chlorodiphenylamine-2-carboxylic Acid.[10]—One hundred grams (0.52 mole) of 2,4-dichlorobenzoic acid, 60 g. (0.64 mole) of aniline, 82 g. (0.59 mole) of potassium carbonate, 3–5 g. of copper oxide (precipitated powder), and 250 ml. of isoamyl alcohol were refluxed three hours. The hot solution was steam distilled until all of the alcohol and some basic oil came over. The hot residual solution was diluted to 3–4 liters with hot water and decolorized with carbon. The filtrate was acidified with dilute hydrochloric acid, and filtered. The yield was 103–115 g. of crude 5-chlorodiphenylamine-2-carboxylic acid. Since purification was not necessary at this step and would diminish over-all yields, no attempt was made to isolate the pure amino acids.

(3) Corse, Shonle and Bryant, THIS JOURNAL, **68**, 1905, 1911 (1946), reported previous series in which the nucleus was held constant and the side chain was varied.

(4) Performed by K. K. Chen, C. L. Rose and R. C. Anderson of these laboratories, using *Plasmodium Lophurae*.

(5) Hall and Turner, *J. Chem. Soc.*, 694 (1945).

(6) "Organic Syntheses," Coll. Vol. II, p. 16, (1943).

(7) Kremer and Bendich, THIS JOURNAL, **61**, 2659 (1939).

(8) French Patent 738,157.

(9) Ullmann, *Ann.*, **355**, 312 (1907).

(10) Ullmann and Wagner, *ibid.*, **355**, 359 (1907).

The crude amino acids were ring closed to the corresponding 9-chloroacridines[11] and these then reacted with excess 5-diethylamino-2-aminopentane in phenol at 100–110° for one to two hours. The reaction mixtures were decomposed with excess sodium hydroxide solution and extracted with ether. The ether layers were washed and extracted with 5% acetic acid. The bases were liberated from the acetate solutions with sodium hydroxide, taken up in ether and heated eventually at 100° at 15 mm. to remove excess 5-diethylamino-2-aminopentane. Dry hydrogen chloride passed into the solutions of the bases in dry ether gave the anhydrous hydrochlorides which were extremely hygroscopic. The melting points of the anhydrous salts varied widely with slight changes in hydrogen chloride content and were therefore meaningless. Table I lists the acridines prepared in this manner.

TABLE I

9-(4'-DIETHYLAMINO-1'-METHYBUTYLAMINO)-ACRIDINES

Substituents (Fig. 1)	Yield, %[a]	Formula	Nitrogen, % Calcd.	Found[b]
None	71[c]	$C_{23}H_{29}N_3 \cdot 2HCl$	10.29	9.60
2-Cl[d]	34	$C_{23}H_{28}ClN_3 \cdot 2HCl$	9.49	9.68
3-Cl[e]	29	$C_{23}H_{28}ClN_3 \cdot 2HCl$	9.49	9.23
4-Cl	24	$C_{23}H_{28}ClN_3 \cdot 2HCl$	9.49	9.69
4-CH_3	37	$C_{24}H_{31}N_3 \cdot 2HCl$	9.95	9.85
4-OCH_3	15	$C_{24}H_{31}N_3O \cdot HCl$	10.48	10.44
1,3-diCl[g]	7[f]	$C_{23}H_{27}Cl_2N_3 \cdot 2HCl \cdot H_2O$	8.48	8.50
2-OCH_3-4-Cl	30[f]	$C_{24}H_{30}ClN_3O \cdot 2HCl$	8.88	8.81
4-OCH_3-6-Cl	59	$C_{24}H_{30}ClN_3O \cdot 2HCl$	8.88	8.43
4-OCH_3-1-CH_3	38	$C_{25}H_{33}N_3O \cdot HCl$	10.10	9.95
2-Cl-4-CH_3	17[f]	$C_{24}H_{30}ClN_3 \cdot 2HCl$	9.20	8.42
3-Cl-4-CH_3	23[f]	$C_{24}H_{30}ClN_3 \cdot 2HCl$	9.20	8.43
2-Br-4-CH_3	11	$C_{24}H_{30}BrN_3 \cdot 2HCl$	8.38	8.16
2-CH_3O-4,6-diCl	29	$C_{25}H_{29}Cl_2N_3O \cdot 2HCl$	8.28	8.21
4-CH_3-3,6-diCl	15	$C_{24}H_{29}Cl_2N_3 \cdot 2HCl$	8.56	8.59
2,4,6-triCl[h]	2	$C_{22}H_{26}Cl_3N \cdot 2HCl \cdot H_2O$	7.94	7.95

[a] Based on 2-chloro or 2,4-dichlorobenzoic acid unless otherwise noted. [b] The samples were dried *in vacuo* for two weeks over potassium hydroxide before analysis. [c] Based on 9-chloroacridine. [d] Previously reported, U. S. Patent 2,077,249. [e] Previously reported, German Patent 571,449. [f] Based on 2-bromobenzoic acid. [g] Recrystallized from ethanol–water–ether, m. p. 138–142°. [h] Recrystallized from ethanol–water–ether, m. p. 158–161°.

(11) "Organic Syntheses," **22**, 5 (1942).

LILLY RESEARCH LABORATORIES
INDIANAPOLIS 6, INDIANA RECEIVED FEBRUARY 6, 1948

Ethyl Acetoacetate 4-Nitrophenylhydrazone and 1-(4'-Nitrophenyl)-3-methylpyrazolone-5

BY WARD C. SUMPTER AND PHIL H. WILKEN

The interaction of equimolecular proportions of ethyl acetoacetate and 4-nitrophenylhydrazine at steam-bath temperature in either the presence or absence of ethanol as a solvent yields ethyl acetoacetate 4-nitrophenylhydrazone (I), m. p. 118°, and not 1-(4'-nitrophenyl)-3-methylpyrazolone-5 (II), m. p. 218°, as stated in the literature.[1]

The nitrophenylhydrazone (I) was converted into the pyrazolone (II) by refluxing a solution of I in glacial acetic acid for five hours at steam-bath temperature. Heating I at steam-bath temperature for fifteen minutes with concentrated hydrochloric acid accomplished the same transformation. Similarly II was obtained when ethyl ace-

(1) Altschul, *Ber.*, **25**, 1853 (1892), via Huntress-Mulliken, "Identification of Pure Organic Compounds, Order 1," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 255.

toacetate and 4-nitrophenylhydrazine were refluxed together in equimolecular quantities in glacial acetic acid as solvent. The pyrazolone (II) was also obtained when the condensation of ethyl acetoacetate and 4-nitrophenylhydrazine was carried out in the presence of concentrated hydrochloric acid with or without the addition of ethanol.

The samples of II obtained in these several procedures were identified by comparison with an authentic sample prepared by the nitration of 1-phenyl-3-methylpyrazolone-5 as described in German Patent 61794.[2]

Experimental

Ethyl Acetoacetate 4-Nitrophenylhydrazone (I).—A mixture of 15.3 g. (0.1 mole) of 4-nitrophenylhydrazine and 13.0 g. (0.1 mole) of ethyl acetoacetate with or without the addition of a small quantity of ethanol as solvent was heated under reflux on the steam-bath for several hours. The orange colored crystalline product which separated on cooling was purified by crystallization from 95% ethanol; m. p. 118°.

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: N, 15.84. Found: N, 15.85, 15.76.

1-(4′-Nitrophenyl)-3-methylpyrazolone-5 (II). **A.**—A sample of ethyl acetoacetate 4-nitrophenylhydrazone (5 g.) was treated with sufficient glacial acetic acid to dissolve it and the resulting solution heated under reflux at steam-bath temperature for five hours. The yellow crystalline product which separated on cooling was purified by crystallization from 95% ethanol from which it separated as light yellow crystals; m. p. 218°. Heating the hydrazone (I) for fifteen minutes at steam-bath temperature with concentrated hydrochloric acid brought about the same transformation.

B.—A mixture of 7.65 g. (0.05 mole) of 4-nitrophenylhydrazine, 6.5 g. (0.05 mole) of ethyl acetoacetate and 25 g. of glacial acetic acid was heated under reflux at steam-bath temperature for five hours. The product which separated on cooling was crystallized from 95% ethanol from which it separated as light yellow crystals; m. p. 218°. The pyrazolone (II) was also obtained when a mixture of ethyl acetoacetate (0.05 mole) and 4-nitrophenylhydrazine (0.05 mole) was heated in the presence of 2 ml. of concentrated hydrochloric acid either with or without the addition of ethanol.

C.—The compound was prepared from 1-phenyl-3-methylpyrazolone-5 by nitration according to the procedure given in German Patent 61794[2]; light yellow crystals; m. p. 218°.

The identity of the samples prepared by procedures A, B and C was established by melting point methods. The melting points reported herein are uncorrected.

Anal. Calcd. for $C_{10}H_9N_3O_3$: N, 19.17. Found: N, 18.74, 18.80.

(2) *Friedländer*, **3**, 926.

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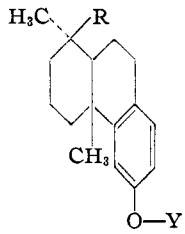
RECEIVED JANUARY 10, 1948

Studies on Resin Acids. III. A Direct Reduction of Podocarpic Acid[1]

BY HAROLD H. ZEISS, CHESTER E. SLIMOWICZ AND VARSENIG Z. PASTERNAK

The constitution of the naturally occurring podocarpic acid (I) has suggested this resin acid as an unusually attractive starting material for the preparation of compounds having structural and perhaps physiological similarity to estradiol. One such compound is the hitherto unknown podocarpinol (II), the preparation of which is described in one step from podocarpic acid in this paper.



I, R = COOH; Y = H
II, R = CH_2OH; Y = H
III, R = COOCH; Y = CH_3
IV, R = COCl; Y = CH_3
V, R = CH_2OH; Y = CH_3

The direct reduction of the carboxylic acid group of the resin acids is usually attended by more or less difficulty, depending upon the configuration of these groups at the C_4 position. The *trans* acids,[2] represented by abietic acid, are less hindered and therefore more easily reduced than the *cis* acids,[2] represented by agathic and podocarpic acids, which are quite resistant to reaction owing to the extremely large effect of steric hindrance. While methyl abietate responds readily to a forced Bouveault–Blanc reduction, the methyl ester of isonoragathic acid is converted to isonoragathenol in very poor yield.[3] Alternately Campbell and Todd[4] have used an indirect method for reducing the O-methyl derivative of podocarpic acid to O-methylpodocarpinol *via* the acid chloride and the aldehyde.

It has been found that lithium aluminum hydride,[5] a compound recently discovered by Schlesinger and co-workers[6] and developed by Nystrom and Brown,[7] converts podocarpic acid directly to podocarpinol in satisfactory yield (56%). Under the same experimental conditions the methyl ester (III) and the acid chloride (IV) of O-methylpodocarpic acid also react with lithium aluminum hydride to give, after hydrolysis of the metal complex, O-methylpodocarpinol (V). The identity of podocarpinol is established by methylation to the known O-methylpodocarpinol.

Although the rate of reaction of lithium aluminum hydride with podocarpic acid is slow, it appears that the reduction of hindered acids with this reagent is not unreasonably limited by steric effects.

Experimental

Podocarpinol (II).—A solution of 8 g. of lithium aluminum hydride in 300 ml. of dry ether was placed in a one-liter flask equipped with dropping funnel, reflux condenser and mercury seal stirrer. All outlets were provided with calcium chloride tubes to exclude moisture during the reaction. To this solution was added dropwise with stirring 7 g. of podocarpic acid (m. p. 194–196°) dissolved in 150 ml. of ether. The mixture was then

(1) Paper II: Zeiss, THIS JOURNAL, **70**, 858 (1948).

(2) Zeiss, *Chem. Rev.*, **42**, 163 (1948).

(3) Ruzicka and Jacobs, *Rev. trav. chim.*, **57**, 509 (1938).

(4) Campbell and Todd, THIS JOURNAL, **64**, 928 (1942).

(5) Metal Hydrides, Inc., Beverly, Mass.

(6) Finholt, Bond and Schlesinger, THIS JOURNAL, **69**, 1199 (1947).

(7) Nystrom and Brown, *ibid.*, **69**, 1197; **69**, 2548 (1947).