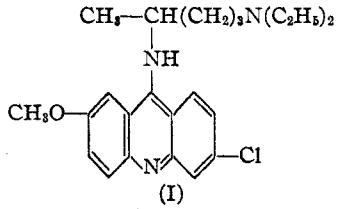
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

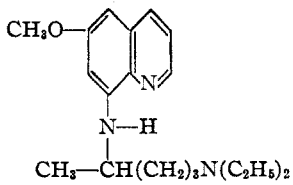
Pyrryl Derivatives of Pyridine, Quinoline and Acridine

BY HENRY GILMAN, C. G. STUCKWISCH[1] AND J. F. NOBIS

In connection with some studies on antimalarials patterned after atebrin (I) and plasmochin (II), a series of compounds has been prepared in which the dialkylaminoalkylamino sidechains have been replaced by pyrryl groups like 2,5-dimethylpyrryl.

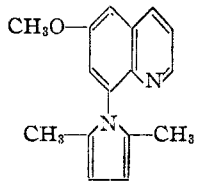


(I)

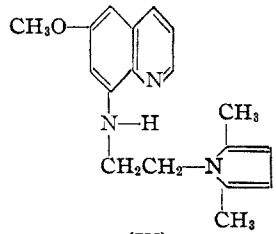


(II)

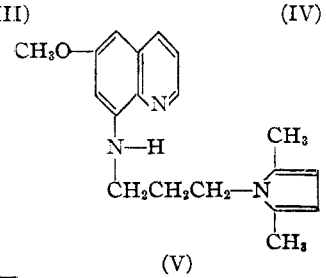
The simple 2,5-dimethylpyrryl types were made by condensation of the amine with acetonylacetone.[2] The yields in this reaction were generally satisfactory and reached 93% in the preparation of 6-methoxy-8-(2,5-dimethylpyrryl-1)-quinoline[3] (III). In order to examine the effect of removing the 2,5-dimethylpyrryl group from the parent nucleus, 6-methoxy-8-[β-(2,5-dimethylpyrryl-1)-ethylamino]-quinoline (IV) and 6-methoxy-8-[γ-(2,5-dimethylpyrryl-1)-propylamino]-quinoline (V) were prepared by condensing the appropriate aminoalkylamino compounds with acetonylacetone.



(III)

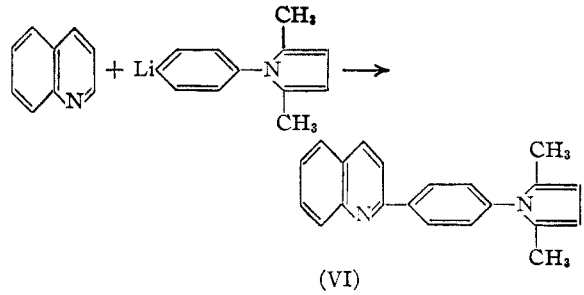


(IV)



(V)

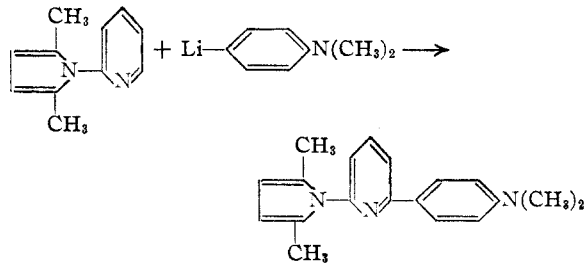
Another variant in the introduction of the 2,5-dimethylpyrryl group involved the addition of *p*-(2,5-dimethylpyrryl-1)-phenyllithium[4a] to pyridine, 8-methylquinoline and quinoline. An illustration is the following reaction, the intermediate dihydro product (formed by addition of the RLi compound to the anil linkage) being oxidized by nitrobenzene to (VI).



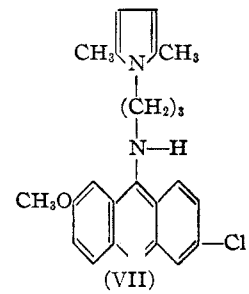
(VI)

Compound (VI) was also formed by the condensation of 2-*p*-aminophenylquinoline with acetonylacetone.

Organolithium compounds were also used to introduce a basic substituent into pyridine[4b] and quinoline types already containing the 2,5-dimethylpyrryl group.



With the atebrin types, the 9-chlorine in 2-methoxy-6,9-dichloroacridine was replaced by



(VII)

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(2) Hazelwood, Hughes and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 92 (1937) [*C. A.*, **32**, 1695 (1938)]; see, also, Paal and Schneider, *Ber.*, **19**, 558 (1886).

(3) This particular amine has just been described by Coates, Cook, Heilbron and Lewis, *J. Chem. Soc.*, 419 (1943), who obtained it in a 23% yield.

(4) (a) Gilman and O'Donnell, THIS JOURNAL, **66**, 840 (1944); (b) for a series of related pyridine types patterned after open-models of atebrin, see Edward and Gilman, *ibid.*, **68**, in press (1946).

TABLE I

2,5-DIMETHYLPYRROLES FROM ACETONYLACETONE

Product	Crystallizing solvent	M. p., °C.	Yield, %	N %, Calcd.	N %, Found
1-(γ-Diethylaminopropyl)-2,5-dimethylpyrrole[a]		B. p., 146° (16 mm.)	50	13.46	13.45
1-(4′-Benzenesulfonamido)-2,5-dimethylpyrrole[b]	Ethanol	134–135°	33	11.20	11.31
1-(*p*-Methoxyphenyl)-2,5-dimethylpyrrole[c]	Ethanol	64	78	6.96	6.87
1-(*m*-Trifluoromethylphenyl)-2,5-dimethylpyrrole	Dil. methanol	42	82	5.85	5.80
1-(*p*-Arsonophenyl)-2,5-dimethylpyrrole[d]	Ethanol	230 d.	70	4.74	4.79
6-Methoxy-8-(2,5-dimethylpyrryl-1)-quinoline	Ethanol	146–147	93	5.75	5.72
2-(2,5-Dimethylpyrryl-1)-pyridine[e]		B. p., 146° (15 mm.)	57	16.28	16.30

[a] The mixture of γ-diethylaminopropylamine (10 g.) and acetonylacetone (14 g.) was refluxed for two hours, and then distilled at 144–146° (15 mm.) to yield 16 g. of product. Redistillation gave 8 g. (50%) distilling at 146° (16 mm.); d^{29}_{27} 0.8999; and $n^{25}D$ >1.7. The 1-(γ-diethylaminopropyl)-2,5-dimethylpyrrole has a skin irritant action. [b] A solution of *p*-aminobenzenesulfonamide (10 g.) and acetonylacetone (7.8 g.) in 15 cc. of ethanol and 3 cc. of acetic acid was refluxed for five hours. [c] In this preparation and the two compounds which follow in the table, the procedure was that described for the synthesis of 6-methoxy-8-(2,5-dimethylpyrryl-1)-quinoline, and the reactions were carried out in 0.5 *M* quantities. [d] See, Ehrlich, *Ber.*, **42**, 17 (1902). [e] A mixture of 37 g. (0.5 mole) of 2-aminopyridine, 57 g. (0.5 mole) of acetonylacetone and 3 cc. of hydrochloric acid was refluxed for four hours. The oil which formed after pouring upon ice was separated and then fractionally distilled; b. p., 146° (15 mm.); d^{29}_{27} 1.058; $n^{25}D$ 1.5710. Molecular refraction: calcd., 53.1; found, 53.41.

the pyrryl, piperidyl, 2,5-dimethylpyrryl, and γ-(2,5-dimethylpyrryl-1)-propylamino groups, (V-II) being formed from the last mentioned reaction.

Experimental

2,5-Dimethylpyrroles by Condensation with Acetonylacetone.—Table I lists a series of 2,5-dimethylpyrroles prepared from acetonylacetone. Two other condensations follow the table.

6-Methoxy-8-(2,5-dimethylpyrryl-1)-quinoline was prepared by refluxing a mixture of 17.4 g. (0.1 mole) of 6-methoxy-8-aminoquinoline and 12.4 g. (0.1 mole) of acetonylacetone for two and one-half hours. The reaction flask was provided with an air condenser to permit escape of the water formed in the reaction. The mixture was poured into ice water, and the solid which separated was collected on a filter, dried, and then crystallized from 95% ethanol. The yield of product, melting at 146–147°, was 24.5 g. (93%). In an earlier experiment, the material obtained when the reaction mixture was poured into water was dissolved in dilute hydrochloric acid, filtered, and then precipitated with dilute ammonium hydroxide. The solid was filtered and then crystallized from 95% ethanol. Inasmuch as no apparent advantage was gained in purification by this additional step, it was omitted in most of the subsequent experiments.

The amine forms a picrate which melts at 114–115° after crystallization from ethanol.

Anal. Calcd. for $C_{17}H_{15}O_7N_5$: N, 17.50. Found: N, 17.56.

6-Methoxy-8-[β-(2,5-dimethylpyrryl-1)-ethylamino]-quinoline Hydrochloride.—A mixture of 6.5 g. (0.03 mole) of 6-methoxy-8-(β-aminoethylamino)-quinoline[5] and 3.72 g. (0.03 mole) of acetonylacetone was refluxed for two hours and then poured into ice water. The tarry residue which separated was dissolved in ether, and the ether extracted with dilute hydrochloric acid. The aqueous extract was neutralized with ammonium hydroxide; the mixture extracted with ether; the ether layer dried over sodium sulfate; and the hydrochloride precipitated by hydrogen chloride. The yield of hydrochloride (after drying over sodium hydroxide in a desiccator for 48 hours) was 4 g. (40%). The brownish hydrochloride is very hygroscopic and decomposes on heating.

Anal. Calcd. for $C_{18}H_{22}ON_3Cl$: N, 12.18. Found: N, 12.47.

6-Methoxy-8-[γ-(2,5-dimethylpyrryl-1)-propylamino]-quinoline Hydrochloride.—A mixture of 9 g. (0.03 mole) of 6-methoxy-8-(γ-aminopropylamino)-quinoline[5] was condensed with acetonylacetone in accordance with the procedure described above for the ethylamino compound. The yield of hydrochloride, which decomposes on heating, was 3.5 g. (34%).

Anal. Calcd. for $C_{19}H_{24}ON_3Cl$: N, 12.11. Found: N, 11.90.

2-(2,5-Dimethylpyrryl-1)-6-(*p*-dimethylaminophenyl)-pyridine.—To a filtered solution of *p*-dimethylaminophenyllithium (prepared in nitrogen from 0.1 mole of *p*-bromodimethylaniline) was added 17 g. (0.1 mole) of 2-(2,5-dimethylpyrryl-1)-pyridine in 35 cc. of ether. At the end of two hours, a color test[6] was negative. The intermediate dihydro derivative, formed by the addition of the RLi compound to the anil linkage, was oxidized by passing dry air over the stirred solution for four hours. Subsequent to hydrolysis, filtration, ether extraction, and removal of the ether there was obtained a solid which melted at 185–186° after crystallization from ethanol. The yield was 5 g. (17%).

Anal. Calcd. for $C_{19}H_{21}N_3$: N, 14.41. Found: N, 14.35.

2-(*p*-Dimethylaminophenyl)-6-methoxy-8-(2,5-dimethylpyrryl-1)-quinoline.—A solution of 7.5 g. (0.03 mole) of 6-methoxy-8-(2,5-dimethylpyrryl-1)-quinoline in 150 cc. of ether was added dropwise to a solution of *p*-dimethylaminophenyllithium prepared from 6 g. (0.03 mole) of *p*-bromodimethylaniline. After two hours, the mixture was hydrolyzed, the ether layer was dried, and the ether removed under reduced pressure. The residue was refluxed for one-half hour with 50 cc. of nitrobenzene to oxidize the dihydro compound. The bright yellow crystals which separated on cooling were filtered and then crystallized from 95% ethanol to give 4 g. (32%) of product melting at 185–186°.

Anal. Calcd. for $C_{24}H_{25}ON_3$: N, 11.32. Found: N, 11.35.

2-[*p*-(2,5-Dimethylpyrryl-1)-phenyl]-8-methylquinoline.—To 0.07 mole of *p*-(2,5-dimethylpyrryl-1)-phenyllithium[4] in 150 cc. of ether, cooled to 0°, was added 10 g. (0.07 mole) of 8-methylquinoline in 50 cc. of ether. When addition was completed, the mixture was stirred for fifteen minutes at 0° and then for thirty minutes at room temperature. The mixture was hydrolyzed and, after removing the dried ether, the residue was refluxed in 50 cc. of nitrobenzene for thirty minutes. The nitrobenzene was removed by steam distillation and the residue was crystallized from a benzene–petroleum ether (b. p., 60–68°) mix-

(5) Baldwin, *J. Chem. Soc.*, 2963 (1929).

(6) Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925).

ture to give 5 g. (23%) of a yellow compound melting at 124–125°.

Anal. Calcd. for $C_{22}H_{20}N_2$: N, 8.97. Found: N, 8.86.

2-[*p*-(2,5-Dimethylpyrryl-1)-phenyl]-quinoline.—From *p*-(2,5-dimethylpyrryl-1)-phenyllithium and quinoline, by procedures like those described in the preceding preparation, was obtained a 5% yield of compound melting at 149–150° after crystallization from ethanol. The nitrobenzene oxidation of the dihydro compound was a little troublesome in this preparation. The 2-[*p*-(2,5-dimethylpyrryl-1)-phenyl]-quinoline was shown to be identical (mixed melting point) with the compound obtained earlier[7] by condensation of 2-(*p*-aminophenyl)-quinoline with acetonylacetone.

Anal. Calcd. for $C_{21}H_{18}N_2$: N, 9.51. Found: N, 9.53.

The picrate after crystallization from ethanol melted at 176–177°.

Anal. Calcd. for $C_{27}H_{21}O_7N_5$: N, 13.2. Found: N, 13.2.

2-[*p*-(2,5-Dimethylpyrryl-1)-phenyl]-pyridine.—From *p*-(2,5-dimethylpyrryl-1)-phenyllithium and pyridine (8 g.) was obtained (subsequent to dry air oxidation of the dihydro compound) 6 g. (24.2%) of compound distilling at 170–172° (2 mm.) and melting at 93–94° after recrystallization from petroleum ether (b. p., 77–115°).

Anal. Calcd. for $C_{17}H_{16}N_2$: N, 11.29. Found: N, 11.22.

9-Substituted-2-methoxy-6-chloroacridines.—The condensations of pyrrole, 2,5-dimethylpyrrole, and piperidine with 2-methoxy-6,9-dichloroacridine were carried out in essential accordance with the procedure of Mueller and Hamilton.[8] In each case, 8.3 g. (0.03 mole) of 2-methoxy-6,9-dichloroacridine was heated with 10 cc. of the amine for four hours at 140°. The mixture, which solidified on cooling, was transferred to a suction filter to remove the excess of amine, and the product was recrystallized from 95% ethanol.

In these condensations, there was more resinification with 2,5-dimethylpyrrole than with pyrrole; and more with pyrrole than with piperidine. The solubilities in 95% ethanol were in the reverse order: 2,5-dimethylpyrryl- > pyrryl- > piperidyl.

The results are contained in Table II, and the additional related preparation which follows the table.

(7) Unpublished studies by S. M. Spatz.

(8) Mueller and Hamilton, THIS JOURNAL, **65**, 1017 (1943).

TABLE II

9-SUBSTITUTED-2-METHOXY-6-CHLOROACRIDINES

Product, 2-methoxy-6-chloro-9-	M. p., °C.	Yield, %	N, % Calcd.	N, % Found
-(1-pyrryl)acridine	245–246	65	9.07	9.20
(2,5-dimethylpyrryl-1)-acridine	225–226	40	8.32	8.16
-(1-piperidyl)acridine	136–137	85	8.57	8.73

2-Methoxy-6-chloro-9-[γ-(2,5-dimethylpyrryl-1)-propylamino]-acridine.—A mixture of 8.34 g. (0.03 mole) of 2-methoxy-6,9-dichloroacridine, 5 g. of phenol, and 5 cc. of 1-(γ-aminopropyl)-2,5-dimethylpyrrole was heated at 130° for eight hours. The solid obtained on cooling was washed with 10% sodium hydroxide to remove the phenol, and the residue was recrystallized from a benzene–petroleum ether mixture to give 4 g. (34%) of product melting at 185–186°.

Anal. Calcd. for $C_{23}H_{24}ON_3Cl$: N, 10.66. Found: N, 10.47.

Acknowledgment.—The authors are grateful to Drs. R. J. Porter and L. T. Coggeshall of the University of Michigan, for the antimalarial tests, the results of which will be published elsewhere.

Summary

A series of pyrryl derivatives of pyridine, quinoline and acridine has been made by reactions involving: (1) condensation of amines with acetonylacetone; (2) condensation of reactive chlorine with pyrrole and 2,5-dimethylpyrrole; (3) addition of RLi compound containing a basic group to pyridines and quinolines having the 2,5-dimethylpyrryl group as a substituent; and (4) addition of *p*-(2,5-dimethylpyrryl)-phenyllithium to the anil linkage of pyridines and quinolines.

AMES, IOWA RECEIVED[9] FEBRUARY 17, 1944

(9) This manuscript was originally received on February 17, 1944 and after examination by the Editorial Board was accepted for publication in the Journal. It was, however, referred to the National Defense Research Committee and at their request was withheld from publication, in a confidential file, until clearance was granted on October 8, 1945.—*The Editor.*

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF GEORGIA]

The Synthesis of Several Dinitrodiphenylthiocarbazides and a Dinitrodiphenylthiocarbazone

BY ALFRED W. SCOTT AND C. R. SPELL[1]

Diphenylthiocarbazide and diphenylthiocarbazone have been found to give precipitates or color reactions with aqueous solutions of seventeen and nine inorganic cations, respectively.[2] The introduction of a nitro group, especially in the para position, into 1-allyl-4-phenyl thiosemicarbazide[3] has been found to increase the sensitivity of this reagent in the detection of silver and of mercury.

The purpose of this investigation was to prepare several isomeric dinitrodiphenylthiocarbazides and a dinitrodiphenylthiocarbazone, and to observe the influence of the position of the nitro groups upon the sensitivity of the reagents.

Distilled water solutions (1 g./liter) of the C. P. metallic nitrates of most of the cations usually

(1) Constructed from a thesis by C. R. Spell, presented to the Graduate Faculty of the University of Georgia, in partial fulfillment of the requirements for the degree of Master of Science.

(2) "Tables of Reagents for Inorganic Analysis," Akademische Verlagsgesellschaft m. b. H., Leipzig, 1938; Ibert Mellan, "Organic Reagents in Inorganic Analysis," The Blakiston Co., Philadelphia, 1941; K. Heller and P. Krumholz, *Mikrochemie*, **8**, 33 (1930); P. Krumholz and F. Hönel, *Mikrochim. Acta*, **3**, 306 (1936); John H. Yoe and L. A. Sarver, "Organic Analytical Reagents," John Wiley and Sons, New York, 1941.

(3) Alfred W. Scott and J. T. Andrews, THIS JOURNAL, **64**, 2873 (1942).