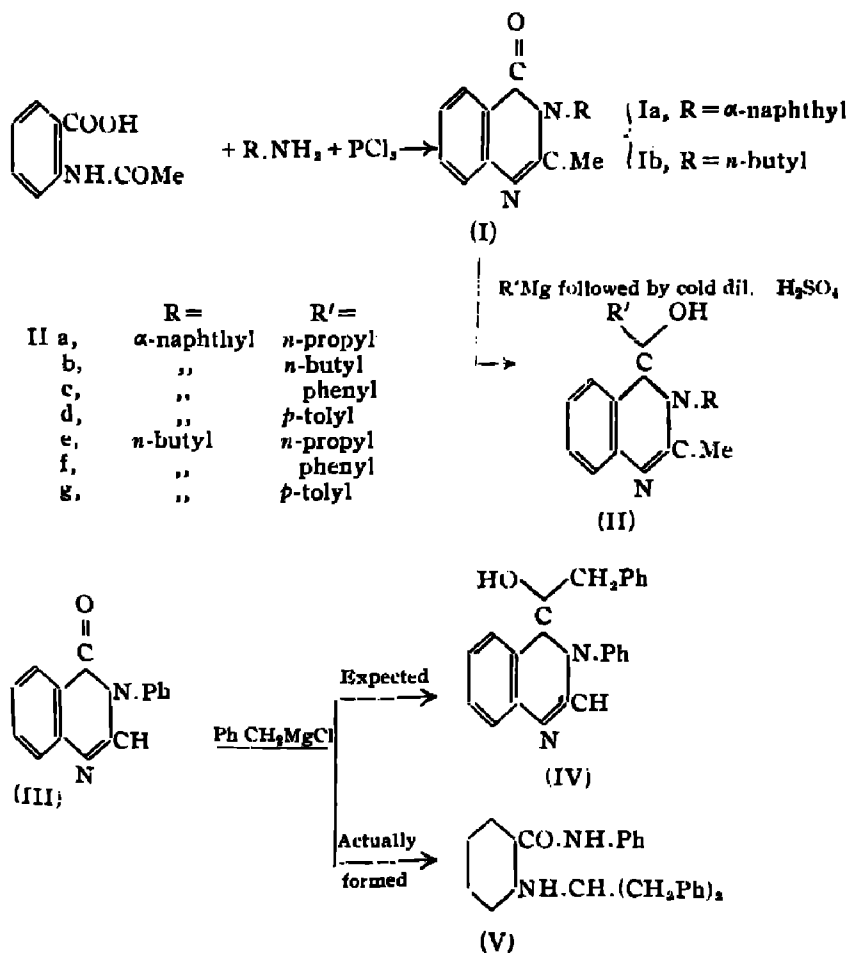


SYNTHESIS OF 4-QUINAZOLONES. PART II

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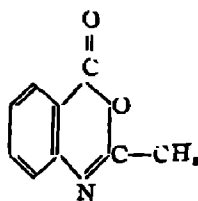
Two new 4-quinazolones have been prepared from which seven 4-quinazolols have been obtained with a view to testing them for possible analgesic action.

In a previous communication (Sen and Siddhu, this *Journal*, 1948, 25, 437) the preparation of 2-methyl-3-phenyl-4-quinazolone and its conversion into three 4-substituted quinazolols were reported. In this paper the work has been extended to the preparation of 2-methyl-3- α -naphthyl- and 2-methyl-3-*n*-butyl-4-quinazolones from which seven 4-quinazolols have been obtained by the action of different alkyl or aryl magnesium halides on the quinazolones, followed by decomposition of the Grignard complex with dilute acid. The 4-quinazolones were prepared by following the general method of Grimmel, Gunther and Morgan (*J. Amer. Chem. Soc.*, 1946, 68, 548).

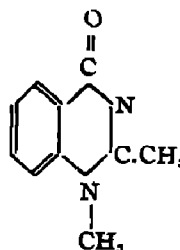


Koelsch (*J. Amer. Chem. Soc.*, 1945, **67**, 1718) studied the action of benzylmagnesium chloride on 3-phenyl-4-quinazoline (III) and has established that the expected 4-quinazolol (IV) is not formed. The reaction follows an anomalous course and results in the formation of the open-chain N-($\beta\beta$ -diphenylisopropyl)-anthranilamide (V).

The question arises whether the reaction products obtained by the action of different Grignard reagents on 4-quinazolones, as reported in this paper and the previous paper (Sen and Sidhu, *loc. cit.*), are the normally expected 4-quinazolols or the open-chain compounds formed by rupture of the heterocyclic ring as in the above case. Koelsch (*loc. cit.*) has drawn attention to the fact that benzylmagnesium chloride reacts with acetantranil (VI) and with 1:2-dimethyl-4-quinazoline (VII) to give the normally expected alcohols.



(VI)



(VII)

He has offered an explanation of this fact by the development of electrophilic centres at different carbon atoms in the molecule. In compound (III) the electrophilic centre develops at C_2 and attack by R^- (of $R-Mg Br$) takes place at C_2 in preference to C_4 . In (VI) and (VII) C_4 retains electrophilic properties greater than C_2 and hence the normal course of the Grignard addition at C_4 is followed.

The quinazolones studied by us are all substituted at C_2 like (VI) and (VII) and no electrophilic centre other than at C_4 can be developed. Hence the reaction of the Grignard reagent was expected to follow the usual course. The compounds obtained gave salts with aqueous acids and were also acetylated by acetic anhydride in presence of pyridine.

EXPERIMENTAL

N-acetylanthranilic acid was prepared by the action of acetic anhydride on the acid suspended in benzene (Kaufmann, *Ber.*, 1909, **42**, 3482).

2-Methyl-3- α -naphthyl-4-quinazoline.—N-Acetylanthranilic acid (17.9 g., 0.1M), α -naphthylamine (14.3 g., 0.1M) and toluene (175 c.c.) were taken in a 500 c.c. three-necked flask, fitted with a mechanical stirrer, condenser and a dropping funnel and heated in a paraffin-bath (130°). Phosphorus trichloride (4.6 g.) in toluene (25 c.c.) was added through the dropping funnel during a period of 15 minutes and the contents refluxed for 2 hours, after which they were transferred to a two-litre distillation flask and basified with 10% sodium carbonate solution (200 c.c.). The toluene was removed by steam distillation and the residue filtered and washed thoroughly with water and finally

recrystallised from alcohol, m. p: 152° , yield 27 g. (Found: C, 79.0; H, 4.6; N, 9.2. $C_{15}H_{14}ON_2$ requires C, 79.7; H, 4.89; N, 9.79 per cent).

2-Methyl-3-n-butyl-4-quinazolone was obtained from N-acetylanthranilic acid (59.6 g.), *n*-butylamine (24.3 g.) and phosphorus trichloride (14.2 g.) in the same way. The residue after removal of toluene was transferred to a separating funnel and extracted with ether. The ethereal layer was separated and dehydrated over calcium chloride. The ether was then removed and the residue distilled under reduced pressure, when a product distilling at 250° under 8 mm. pressure was obtained, yield 17 g. (Found: C, 72.0; H, 7.1; N, 12.77. $C_{17}H_{18}ON_2$ requires C, 72.2; H, 7.4; N, 12.96 per cent).

Substituted Quinazolols.—The quinazolols were obtained by the action of appropriate Grignard reagents on the quinazolones in the following way.

The Grignard reagent was prepared from magnesium (0.02M) and the alkyl or aryl halide (0.02M) in the usual way. The Grignard reagent was then cooled in ice and the quinazolone (0.02M) suspended in ether was added dropwise. The reaction was over in about 15 minutes after which the contents were refluxed for 2 hours over a water-bath and then decomposed with dilute sulphuric acid. The resulting substance was filtered, washed with water and dried. Most of the quinazolols were recrystallised from alcohol. 3-*n*-Butyl-, 4-phenyl-, 4-propyl- and 4-*p*-tolyl-4-quinazolols were obtained at first as resinous substances which were crystallised with great difficulty from chloroform.

In this way the following quinazolols were obtained.

TABLE I

-4-Quinazolols.	M.p.	Yield.	Carbon		Hydrogen		Nitrogen		M. p. of acetyl deriv.
			Found.	Calc.	Found.	Calc.	Found.	Calc.	
2-Methyl-3 α -naphthyl-									
-4- <i>n</i> -propyl-	190°	70.5%	79.6%	80.0	6.35%	6.6	8.3%	8.48	145°
-4-phenyl-	210°	80.3	82.25	82.4	5.2	5.49	7.5	7.69	145°
-4- <i>n</i> -butyl-	162°	87.2	80.1	80.23	6.7	6.97	8.0	8.14	95°
-4- <i>p</i> -tolyl-	172°	66.1	82.3	82.5	5.7	5.8	7.14	7.4	150°
2-Methyl-3- <i>n</i> -butyl-									
-4-phenyl-	165°	85.0	77.35	77.5	7.3	7.48	9.4	9.52	105°
-4- <i>n</i> -propyl-	170°	86.7	73.65	73.84	9.1	9.23	10.6	10.76	—
-4- <i>p</i> -tolyl-	162°	47.0	77.3	77.5	7.2	7.48	9.4	9.52	—

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