[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Bromination of Some Anilinopyrimidines

BY ARTHUR P. PHILLIPS AND ALLISON MAGGIOLO*

RECEIVED JANUARY 31, 1952

In order to determine the point of preferential attack in electrophilic substitution reactions, the bromination of several 2- and 4-anilinopyrimidines has been studied. When the pyrimidine is activated by two amino groups (including the anilino) substitution is favored at the 5-position of the pyrimidine. When methyls are the only pyrimidine substituents except for the anilino, the anilino nitrogen appears to direct electrophilic attack with about equal facility to the pyrimidine and benzene nuclei.

Because of the well-known easy electrophilic substitutions possible with aniline derivatives and because of the facility with which many of these same substitutions attack the 5-position of many simple amino- and hydroxypyrimidines it was of interest to determine the point of preferential attack in certain anilinopyrimidines. In this work the *bromination* of selected anilinopyrimidine derivatives has been examined because of the relative simplicity of this reaction and it is felt that the knowledge obtained will be of use in many other more complicated synthetic reactions.

The compounds chosen for the bromination studies were: 2-amino-4-anilino-6-methylpyrimidine[1] (III), 2,6-dimethyl-4-anilinopyrimidine[2] (XIV) and 2-anilino-4,6-dimethylpyrimidine (XX).[3] One standard set of bromination conditions was used so that differences in position of attack could be related only to changes in chemical structure. The brominations were carried out in glacial acetic acid solution in the presence of a measured excess of anhydrous sodium acetate. Sodium acetate was used to combine with the strong hydrobromic acid produced during the reaction, thus forestalling any marked change in the cationic nature of the medium which might otherwise have altered the later stages of the reaction.

One equivalent of bromine with 2-amino-4-anilino-6-methylpyrimidine (III) gave exclusively the 5-bromopyrimidine derivative, IV. This was established by an alternative synthesis from 2-amino-4-chloro-5-bromo-6-methylpyrimidine[4] (II) and aniline hydrochloride by the procedure of Banks.[1] The products of the two synthetic routes were identical in chemical and physical properties and both were different from the isomeric 2-amino-4-(4′-bromoanilino)-6-methylpyrimidine (V) obtained by the method of Banks[1] from 2-amino-4-chloro-6-methylpyrimidine (I) and 4-bromoaniline hydrochloride. Bromination of either of these isomeric monobromo derivatives (IV or V) with an additional equivalent of bromine, or reaction of III with two equivalents of bromine all gave the same dibromo derivative, 2-amino-4-(4′-bromoanilino)-5-bromo-6-methylpyrimidine (VI), whose structure was further verified by its synthesis from II and 4-bromoaniline hydrochloride. 2-Amino-4-(4′-chloroanilino)-6-methylpyrimidine[5] (VII) with one equivalent of bromine gave the 5-bromo derivative VIII.

Introduction of a methyl onto the anilino nitrogen does not interfere with the course of this substitution reaction. With one equivalent of bromine 2-amino-4-(N-methylanilino)-6-methylpyrimidine (IX) gave as the only isolated product its 5-bromo derivative (X), although since the yield of purified product was only about 50%, co-formation of the isomeric substance, 2-amino-4-(4′-bromo-N-methylanilino)-6-methylpyrimidine, cannot be excluded. Proof of structure of the isomer isolated was attained by synthesis of X from II and N-methylaniline hydrochloride. With two moles of bromine IX gave an excellent yield of 2-amino-4-(4′-bromo-N-methylanilino)-5-bromo-6-methylpyrimidine (XI).

Bromination of 2,6-dimethyl-4-anilinopyrimidine[2] (XIV) with one mole of bromine gave 2,6-dimethyl-4-anilino-5-bromopyrimidine (XV) while two moles of bromine yielded 2,6-dimethyl-4-(4′-bromoanilino)-5-bromopyrimidine (XVI). The structures of XV and XVI were established by independent syntheses from 2,6-dimethyl-4-chloro-5-bromopyrimidine[6] (XIII) with aniline hydrochloride and 4-bromoaniline hydrochloride, respectively. The 2,6-dimethyl-4-(4′-bromoanilino)-pyrimidine (XVII) when treated with a single equivalent of bromine gave a good yield, based on bromine, of 2,6-dimethyl-4-(2′,4′-dibromoanilino)-5-bromopyrimidine (XVIII) which was also prepared by the interaction of 2,4-dibromoaniline hydrochloride and XIII.

When 2-anilino-4,6-dimethylpyrimidine[3] (XX) was treated with one molecular equivalent of bromine a complex mixture resulted from which were isolated in good yields, based on the bromine used, 2-(4′-bromoanilino)-4,6-dimethylpyrimidine (XXI), 2-anilino-4,6-dimethyl-5-bromopyrimidine (XXII) and 2-(4′-bromoanilino)-4,6-dimethyl-5-bromopyrimidine (XXIII). Reaction of 2-chloro-4,6-dimethylpyrimidine[3] (XIX) with 4-bromoaniline hydrochloride also gave XXI which on the addition of one mole of bromine gave XXIII.

The bromination reaction conditions were varied in a few experiments with one of the anilinopyrimidines (III). One mole of bromine added to III in glacial acetic acid solution with *no* sodium acetate present gave still a nearly quantitative yield

* The work of this author was supported by a grant from the Charles F. Kettering Foundation to the Wellcome Research Laboratories.

(1) C. K. Banks, THIS JOURNAL, **66**, 1131 (1944).

(2) K. F. M. J. Schmidt, *Ber.*, **35**, 1575 (1902).

(3) S. Angerstein, *ibid.*, **34**, 3956 (1901).

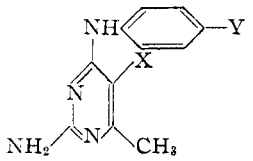
(4) C. C. Price, N. J. Leonard and R. H. Reitsema, THIS JOURNAL, **68**, 766 (1946).

(5) F. R. Basford, F. H. S. Curd, E. Hoggarth and F. L. Rose, *J. Chem. Soc.*, 1354 (1947).

(6) E. Ochiai and Y. Ito, *J. Pharm. Soc. Japan*, **57**, 579 (1937); see C. A., **31**, 6238[6] (1937).

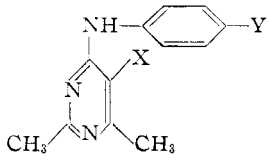
TABLE I

(A) BROMO DERIVATIVES OF 2-AMINO-4-ANILINO-6-METHYLPYRIMIDINE



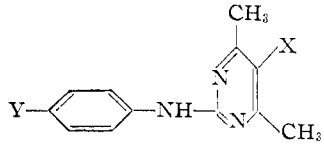
Compound No.	X	Y	Yield (%) by Method[a] A	B	Crystn. solvent[b]	M.p., [c] °C.	Empirical formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
IV	Br	H	100[d,e]	80[f]	Ea.H	152–153	$C_{11}H_{11}BrN_4$	47.3	47.5	4.0	4.2
								N 20.1	N 19.7		
V	H	Br		95[g]	A.Aq	228–229	$C_{11}H_{11}BrN_4$	N 20.1	N 20.0		
VI	Br	Br	100[h]	100[f]	M	192–193[i]	$C_{11}H_{10}Br_2N_4$	36.9	36.9	2.8	2.6
								N 15.6	N 15.4		
VIII	Br	Cl	95[j]		A.Aq	260–261	$C_{11}H_{10}BrClN_4$	N 17.9	N 17.7		
IX	H	H[k]		90[g]	B.H	149–150	$C_{12}H_{14}N_4$	67.3	67.0	6.6	6.5
								N 26.2	N 26.5		
X	Br	H[k]	40[l,m]	80[f]	Ea.H	181–182[j]	$C_{12}H_{13}BrN_4$	49.1	48.9	4.5	4.4
XI	Br	Br[k]	100[l]		M	167–168	$C_{12}H_{12}Br_2N_4$	38.7	39.0	3.3	3.5

(B) Bromo Derivatives of 2,6-Dimethyl-4-anilinopyrimidine



XV	Br	H	70[n]	95[o]	M.Aq	98–99	$C_{12}H_{12}BrN_3$	N 15.1	N 15.0		
						197–198[n]	Picrate	42.6	42.7	3.0	2.9
XVII	H	Br		100[p]	Ea.H	136–137	$C_{12}H_{12}BrN_3$	N 15.1	N 14.8		
					M	207–208[q]	Picrate				
XVI	Br	Br	100[r]	100[o]	M.Aq	160–161[j]	$C_{12}H_{11}Br_2N_3$	40.4	40.0	3.1	2.9
								N 11.8	N 11.8		
XVIII	Br	Br[s]	100[t,u]	100[o]	M.Aq	163–164	$C_{12}H_{10}Br_3N_3$	33.0	33.5	2.3	2.1
								N 9.7	N 9.7		

(C) Bromo Derivatives of 2-Anilino-4,6-dimethylpyrimidine



XXI	H	Br	25[u,v]	100[w]	M.Aq	126–127	$C_{12}H_{12}BrN_3$	N 15.1	N 14.9		
					M	253–254[x]	Picrate	42.6	42.7	3.0	2.5
XXII	Br	H	25[u,v]		M	179–180	$C_{12}H_{12}BrN_3.C_6H_3N_3O_7$	42.6	43.0	3.0	2.6
XXIII	Br	Br	100[y]		M	152–153	$C_{12}H_{11}Br_2N_3$	40.4	40.6	3.1	2.9
								N 11.8	N 11.6		

[a] Preparative methods A and B are those described in the Experimental part: (A) bromination of the anilinopyrimidine; (B) reaction of a chloropyrimidine with an aniline by Banks[1] method. In the brominations (method A) one equivalent of Br_2 was used unless otherwise specified. [b] A, ethanol; Aq, water; B, benzene; Ea, ethyl acetate; H, Skellysolve B; M, methanol. [c] All melting points are uncorrected. [d] From III. [e] This yield of IV was also obtained from III when method A was modified by omitting NaOAc. An additional change, leaving out NaOAc and using 2 equivalents of HCl, gave a complex mixture of mono- and dibromo products from which no pure substance has yet been isolated. [f] From II. [g] From I, 2-amino-4-chloro-6-methylpyrimidine. [h] From III with 2 equivalents of Br_2, and from both IV and V with 1 equivalent of Br_2. [i] The products obtained from the two methods A and B had slightly different melting points, but the ultraviolet absorption spectra of the two products were identical thus confirming that both are the same substance. [j] From VII. [k] These are the N-methylanilino derivatives. [l] From IX. [m] Crude yield was about 100%. [n] Isolated as the picrate from the bromination of XV. The picrate of XV, made from XIII by Method B, gave the same melting point and analysis. [o] From XIII. [p] From XII, 2,6-dimethyl-4-chloropyrimidine. [q] The picrate of XVII. [r] From XIV with 2 equivalents of Br_2. [s] This compound is the 4-(2′,4′-dibromoanilino)-5-bromo-2,6-dimethylpyrimidine. [t] From XVII. [u] Although only one equivalent of Br_2 was used, dibromination occurred. Thus the yield is based on Br_2 as the limiting factor. [v] From XX. Isolated as the picrate. [w] From XIX. [x] The picrate of XXI, made from XIX by method B, had a melting point and analysis nearly identical with that of one of the picrates obtained from XX by method A. [y] From XXI. Also obtained in 50% yield, based on Br_2 used, on the addition of one equivalent of Br_2 to XX.

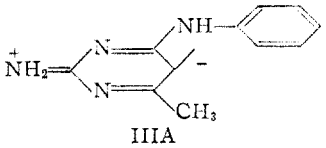
of IV. When the bromination was run in glacial acetic acid with *no* sodium acetate and in the presence of two moles of hydrochloric acid a complex mixture of mono- and dibromo products resulted from which no single pure substance has been isolated as yet.

Discussion

An unsubstituted pyrimidine ring should be inherently much less susceptible to electrophilic attack than an unsubstituted benzene ring because of the well known stronger electronegative nature of the heterocyclic nucleus. Thus, in common with

mono- and polynitrobenzene derivatives, pyridine and quinoline, pyrimidine activates alkyls and halogens in the 2-, 4- and 6-positions for condensation and replacement reactions, respectively.

The preferential substitution on the pyrimidine ring of 2-amino-4-anilino-6-methylpyrimidine (III) can be considered to result from the cumulative activation of the 5-position by electron release from the two amino and the methyl substituents. While the anilino nitrogen tends to activate the 4-position of the benzene ring, it can also activate the 5-position of the pyrimidine. In addition, the 2-amino and the 6-methyl of the pyrimidine should activate strongly the 5-position of the pyrimidine nucleus for attack by electrophilic reagents. The resonance variant shown (IIIA) is only one of those favoring substitution in the 5-position of this pyrimidine.



IIIA

That the combined influence of powerful activators, such as amino, is responsible for favored pyrimidine substitution is borne out by the more nearly equal distribution of substitution between the two rings when the simple amino is replaced by a second methyl group. In these cases the addition of one mole of bromine produces either a mixture of the products of mono-bromination on the pyrimidine or on the benzene nucleus, or gives the 5,4′-dibromo product directly.

Experimental

Intermediates.—Most of the intermediates used are known and references to them are given as they are mentioned in the text.

Preparations of Bromoanilinopyrimidines.—Two general methods were used for the preparation of the various bromoanilinopyrimidines: (A) direct bromination of anilinopyrimidines, and (B) interaction of an aniline (or a bromoaniline) with a chlorobromopyrimidine (or a chloropyrimidine) by a method similar to that of Banks.[1] Details for the individual reactions are summarized in Table I. An illustrative example of each method is described below.

(A) Bromination of Anilinopyrimidines.—To a suspension of 0.01 mole of the anilinopyrimidine in 25 cc. of glacial acetic acid, containing also 0.03 mole of anhydrous sodium acetate, was added dropwise with good mixing a solution of 0.01 mole of bromine in 10 cc. of glacial acetic acid. Bromine color usually disappeared instantly following each addition. When all the bromine had been added the reaction mixture was heated for one hour on a steam-bath. After cooling and diluting with 200 cc. of water, concentrated ammonium hydroxide was added to *p*H 9. The white crystalline precipitate was collected by filtration and was purified by recrystallization from aqueous alcohol or various other solvent combinations.

(B) Interaction of an Aniline and a Chlorobromopyrimidine.—A mixture of 0.01 mole of the chlorobromopyrimidine, 0.01 mole of aniline and 0.01 mole of concentrated hydrochloric acid in 30 cc. of water was heated for two hours at 100°. The reaction solution was then diluted with 100 cc. of water and concentrated ammonia added to *p*H 9. After cooling, the white crystalline product was collected and purified by recrystallization from appropriate solvents.

Acknowledgment.—The authors are indebted to S. W. Blackman and N. Martinez, Jr., for the microanalyses and to Miss Phoebe Lee Graham for some ultraviolet absorption spectra.

TUCKAHOE 7, NEW YORK

[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY OF WESTERN RESERVE UNIVERSITY]

Reactions of Terminally Substituted 1,3-Butadienes with Sulfur Dioxide

BY OLIVER GRUMMITT AND JANET SPLITTER[1]

RECEIVED SEPTEMBER 17, 1951

To determine the cause for the failure of *trans*-1-phenyl-1,3-butadiene to react with sulfur dioxide to give either a cyclic sulfone or a polysulfone, the behavior of the *trans*-isomers of 1-cyclohexyl-, 1-(*p*-nitrophenyl)- and 1-(*p*-anisyl)-1,3-butadiene with sulfur dioxide has been investigated. *trans*-1-Cyclohexyl-1,3-butadiene was made in 40% yield by the thermal decomposition of 1-cyclohexyl-3-acetoxy-1-butene. The isomeric 1-cyclohexylidene-2-butene was also obtained. The cyclohexylbutadiene added sulfur dioxide under the usual conditions to give both a cyclic and polymeric sulfone, thus pointing to the inductive and/or resonance effects of the phenyl group in phenylbutadiene as the critical factors. *p*-Nitrophenylbutadiene formed a cyclic sulfone, not a polysulfone, while *p*-anisylbutadiene formed neither. These results can be explained in terms of a polar mechanism of addition to a *cis*-butadienoid configuration which is energetically difficult if the 2,3-position in the side chain has a high degree of double bond character through resonance effects of the aryl group.

In earlier work on *cis*- and *trans*-1-phenyl-1,3-butadiene[2] the addition reaction with sulfur dioxide to form a cyclic sulfone (a dihydrothiophene-1-dioxide) was tried as a means of identifying and separating the isomers, as had been done successfully with the geometric isomers of piperylene.[3] The phenylbutadienes however did not react with sulfur dioxide, either through addition to form a cyclic sulfone or through copolymerization to a polysulfone. This study was made to explore the causes for this lack of reactivity.

Selected for investigation of their reactions with sulfur dioxide were the related dienes, *trans*-1-cyclohexyl-1,3-butadiene, *trans*-1-(*p*-nitrophenyl)-1,3-butadiene and *trans*-1-(*p*-anisyl)-1,3-butadiene. The behavior of the cyclohexyl compound would show the effect of a relatively large terminal group of non-aromatic character, located in the *trans* position. Only in the case of the piperylenes has the influence of a non-aromatic terminal group (methyl) on the reactivity with sulfur dioxide been determined: the *trans* isomer forms a sulfone readily, the *cis* reacts slowly and with initial

(1) (a) Taken from Janet Splitter's Ph.D. thesis, Western Reserve University, June, 1950. (b) Presented before the Organic Division, A.C.S. Meeting, Chicago, Ill., Sept. 5, 1950.

(2) O. Grummitt and F. J. Christoph, THIS JOURNAL, **73**, 3479 (1951).

(3) D. Craig, *ibid.*, **65**, 1006 (1943).