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579. *Reactions of 2,2-Dialkyl-1,2-dihydroquinolines. Part I. Preparation of 2-Guanidinoquinazolines.*

By J. P. Brown.

1,2-Dihydro-2,2-dimethylquinoline hydrochlorides react with dicyandiamide in boiling aqueous solution to give 2-guanidinoquinazolines and isobutene. The reaction appears to involve attack of the cyanide nitrogen on the 4-position of the dihydroquinoline. Attempts to extend the reaction to other types of cyano-compound failed. Several of the reaction products inhibit the growth of micro-organisms.

The 1,2-dihydro-2,2,4-trimethylquinolines are prepared [1] by heating primary arylamines with acetone in the presence of a catalyst, usually iodine or toluene-*p*-sulphonic acid. According to the arylamine used, there is considerable variation in the rate, yield, and optimum conditions of the reaction and in the nature of the by-products. The simplest member of the series, 1,2-dihydro-2,2,4-trimethylquinoline, is readily available commercially.

[1] Knövenagel, *Ber.*, 1921, **54***B*, 1722.

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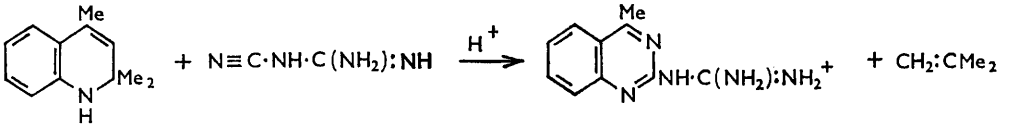
The oily condensation product of *p*-phenetidine and acetone is also used as a rubber antioxidant and antiozonant, and a purified grade ("Santoquin") is an antioxidant for animal feeds. The present work confirms the formulation of this compound as 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline.

Most studies [1,2] of 1,2-dihydro-2,2,4-trimethylquinoline were directed towards establishing its chemical structure. As already mentioned,[3] the transformation now described provides chemical evidence for the 1,2-dihydroquinoline structure, which has been preferred to the alternative formulation, 1,4-dihydro-2,4,4-trimethylquinoline, on spectroscopic evidence,[4] and has recently been confirmed [5] by oxidative degradation of the *N*-acetyl derivative. The main purpose of the present work, however, was a search for biologically active compounds derived from this compound and its analogues.

The transformation described in this Paper was accidentally discovered when 1,2-dihydro-2,2,4-trimethylquinoline was included in a number of arylamines from which biguanides were to be made by the usual method, namely, reaction of the amine hydrochloride with dicyandiamide in boiling aqueous solution. It was thought that this base might fail to react under these conditions since the amino-group is secondary and adjacent to the bulky *gem.*-dimethyl group. Nevertheless, the hydrochloride of a strongly basic compound was rapidly formed. The microanalytical results were, however, in good agreement with the empirical formula, $C_{10}H_{12}ClN_5$, whereas the biguanide hydrochloride would be $C_{14}H_{20}ClN_5$. In view of the difference of C_4H_8, the experiment was repeated with the apparatus vented to a cold trap, in which isobutene (b. p. −6°), characterised by conversion into 2,4,6-tri-t-butylphenol, was collected in 53% yield. The basic product, obtained in 70% yield, was found to be 2-guanidino-4-methylquinazoline, a formulation first suggested by the late Mr. B. E. Wilde. This compound has been prepared [6] by reaction of *o*-aminoacetophenone hydrochloride and dicyandiamide. The identity of specimens made by both routes was established by comparison of their infrared spectra.

The transformation is, therefore, represented:



A number of 1,2-dihydro-2,2,4-trimethylquinolines, substituted in the aromatic nucleus, gave in all cases the corresponding 2-guanidino-4-methylquinazolines in yields up to 76% (Table). Ethanol was sometimes added to the reaction mixture to ensure homogeneity when the dihydroquinoline was feebly basic. Occasionally the guanidinoquinazoline hydrochloride did not separate from the mixture. The free base was then liberated with alkali and freed from resinous material by trituration with ethanol. 1,2-Dihydro-2,2,6-trimethylquinoline [7] also underwent the reaction, giving 2-guanidino-6-methylquinazoline and isobutene, although in poor yield. 1,6-Di-(N^3-cyano-N^1-guanidino)hexane was twice used in place of dicyandiamide. Isobutene was slowly evolved but the products could not be obtained in a crystalline condition.

Attempts to extend the reaction to cyano-compounds other than dicyandiamides, *i.e.*, hydrogen cyanide, cyanamide, acetonitrile, acrylonitrile, benzonitrile, ethyl cyanoacetate, ethyl cyanoformate, trichloroacetonitrile, 2-, 3-, and 4-cyanopyridines, 1-cyano-1,2-dihydro-2-hydroxyquinoline [8] and methyl thiocyanate, failed. No trace of isobutene was detected

[2] Reddelien and Thurm, *Ber.*, 1932, **65***B*, 1511; Cliffe, *J.*, 1933, 1327; Kalnin, *Annalen*, 1936, **523**, 118; Rosser and Ritter, *J. Amer. Chem. Soc.*, 1937, **59**, 2179; Craig, *ibid.*, 1938, **60**, 1458.
[3] Brown, *Chem. and Ind.*, 1960, **9**, 233.
[4] Johnson and Buell, *J. Amer. Chem. Soc.*, 1952, **74**, 4517; Craig and Gregg, *ibid.*, 1955, **75**, 2252.
[5] Elliott and Yates, *J. Org. Chem.*, 1961, **26**, 1287.
[6] Theiling and McKee, *J. Amer. Chem. Soc.*, 1953, **75**, 2252.
[7] Easton and Cassady, *J. Org. Chem.*, 1962, **27**, 4713.
[8] Johnson, *J.*, 1962, 283.

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in any of these experiments. The 1,2-dihydro-2,2,4-trimethylquinoline was partially converted into resinous products as normally happens when it is heated with aqueous acid, but crystalline products could not be isolated. D. J. Beaver and C. C. Tung (personal communication) report that the transformation does, however, proceed with dialkylcyanamides, R_2NCN, to give 2-dialkylaminoquinazolines.

Isobutene could not be detected when 1,2-dihydro-2,2,4-trimethylquinoline hydrochloride was heated in aqueous solution with propargyl alcohol, thiourea, diketen, or ethyl acetoacetate.

1,2,3,4-Tetrahydro-2,2,4-trimethylquinoline hydrochloride did not react with dicyandiamide in boiling aqueous solution, but the alicyclic decahydro-2,2,4-trimethylquinoline gave the normal biguanide. This suggests that there is steric hindrance to the reaction of the secondary amino-group of the dihydroquinoline with the cyano-group of the dicyandiamide. Hence the normal biguanide is not an intermediate in the transformation. Nor is the dihydroquinoline merely a source of *o*-aminoacetophenone, since no trace of isobutene can be detected when the aqueous solution of its hydrochloride is heated in the absence of dicyandiamide. It would seem, therefore, that the nitrogen of the cyano-group reacts with the 3,4-double bond of the base, as in the Ritter reaction of olefins with nitriles.[9] The latter is conducted in media containing concentrated sulphuric acid and this suggested use of such media for the reaction of the simple nitriles, acetonitrile and benzonitrile, with 1,2-dihydro-2,2,4-trimethylquinoline. No product derived from a Ritter reaction on the dihydroquinoline, no free isobutene, and no Ritter product from isobutene could be isolated. This failure is not due to rapid interaction between the dihydroquinoline and sulphuric acid, since, when the base is kept in the acid overnight, a part of it may be recovered. Attempts to prepare a quinazoline from 1,2-dihydro-2,2,4-trimethylquinoline and acetonitrile in perchloric acid solution, or in the presence of stannic chloride, also failed.

The mechanism of this dihydroquinoline–quinazoline transformation and its relation to the Ritter reaction therefore remains obscure. The only two types of cyano-compounds which have been shown to participate, possess strongly basic moieties directly attached to the cyano-group, and these, in the absence of the cyano and other strongly electron-withdrawing groups, would form stable hydrohalides. 1,2-Dihydro-2,2,4-trimethylquinoline base does not react with dicyandiamide in aqueous solution in the presence of catalytic amounts of hydrogen chloride. Highest yields were, in fact, obtained from the dihydroquinoline hydrochloride in the presence of a small excess of hydrogen chloride. The use of a 100% excess reduced the yield.

Attempts to add dicyandiamide in acidic media to 1,2-dihydroquinoline (which resinifies very quickly under these conditions), 2,2,4-trimethylchromen,[10] α-methylstyrene, cinnamylideneaniline, *NN*-dimethylcinnamylamine, 1,2,5,6-tetrahydropyridine, and 3,5-diethoxycarbonyl-1,2-dihydro-2,4,6-trimethylpyridine were also unsuccessful.

The transformation of the *p*-phenetidine–acetone reaction product into a compound whose elemental composition agrees with that of 6-ethoxy-2-guanidino-4-methylquinazoline, confirms the 1,2-dihydroquinoline structure which had been assigned to this product. On the other hand, a product from *p*-phenetidine and isobutyl methyl ketone did not give hydrocarbon on boiling with dicyandiamide in acid. *p*-Ethoxyphenylbiguanide was recovered in good yield, suggesting that this phenetidine–ketone product is the simple anil. A supposed dimer of 1,2-dihydro-2,2,4-trimethylquinoline was recently obtained crystalline by Zalukayev and Zhyeltukhina,[11] who postulate that it is produced by formation of a bond between the 4-position of one molecule, with elimination of the 3,4-double bond, and the 3-position of a second. An alternative structure involves a 4,6-link, and the infrared spectrum of the compound indicates possible 6-substitution. It might be expected that the

[9] Ritter and Minieri, *J. Amer. Chem. Soc.*, 1948, **70**, 4045; Mousseron, Jacquier, and Christol, *Bull. Soc. chim. France*, 1957, 596.
[10] Baker, Floyd, McOmie, Pope, Weaving, and Wild, *J.*, 1956, 2010.
[11] Zalukayev and Zhyeltukhina, *Izvest. V.U.Z. M.V.O. S.S.S.R., Khim i khim. Tekhnol.*, 1962, **5**, 277.

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first structure would give 2-guanidino-4-methylquinazoline with dicyanidamide in acid, but without isobutene formation; whereas the second would give isobutene readily, together with a complex quinolylquinazoline. In fact, only traces of isobutene and a basic product whose spectrum resembled, but was not identical with, that of 2-guanidino-4-methylquinazoline, were obtained. It is possible that dimerisation involves the elimination of the 3,4-double bonds in both molecules of the monomer. Very recently [12] the 4,6-linked dimer has been prepared from 1,2-dihydro-2,2,4-trimethyldihydroquinoline, but this does not seem to be identical with the Russian product. The guanidinoquinazoline transformation has also been of diagnostic value in a study of the halogenation products of 1,2-dihydro-2,2,4-trimethylquinoline, which will be described in Part II.

Many 2-guanidinoquinazolines have antimicrobial activity. Introduction of a 6-t-butyl group gives a wide-spectrum bacteriostat, supressing the gram-positive organism *Staphylococcus aureus* at 20 p.p.m. in nutrient agar, and gram-negative *Pseudomonas aeruginosa* at 200 p.p.m, Halogeno-, methoxy-, or ethoxy-groups also raise activity, larger alkoxy groups lower it.

It was found possible to convert the 2-guanidino-group into an amino-group with hot aqueous alkali, but yields did not exceed 50%. The guanidino-group condenses, as would be expected, with ethyl acetoacetate and with acetylacetone, with the formation of a second heterocyclic ring, presumably that of pyrimidine.

Experimental

2-Guanidino-4-methylquinazoline.—A solution of 1,2-dihydro-2,2,4-trimethylquinoline (8·65 g.) and dicyandiamide (5 g.) in concentrated hydrochloric acid (6·2 ml.) and water (27 ml.) was boiled for 30 min. After cooling, the crystals of *2-guanidino-4-methylquinazoline hydrochloride* (8·3 g., 70%), m. p. 328—330° (decomp. with darkening above 300°), were filtered off and washed with dilute hydrochloric acid. (2-Guanidinoquinazolines are far less soluble in dilute hydrochloric acid than in water or concentrated acid.) The hydrochloride was recrystallised from dilute hydrochloric acid, forming needles (m. p. unchanged) (Found: C, 50·6; H, 5·2; N, 29·7. $C_{10}H_{12}N_5Cl$ requires C, 50·5; H, 5·1; N, 29·9%). The infrared spectrum was identical with that of an authentic specimen.

Isobutene (1·5 g., 53%), b. p. −6°, was collected in a cold trap. The liquid (0·98 g.) was allowed to vaporise into phenol (3·3 g.), mixed with concentrated sulphuric acid (0·17 g.), and heated to 75°. The mixture partially solidified and, by filtration and crystallisation from ethanol, 2,4,6-tri-t-butylphenol (0·64 g.), m. p. 120—125°, was obtained. Repeated recrystallisation raised the melting point to 129—132°, undepressed by admixture with an authentic specimen (Found: C, 82·3; H, 11·2. Calc. for $C_{18}H_{30}O$: C, 82·4; H, 11·5%).

The free base was recovered from an aqueous solution of the quinazoline hydrochloride by pouring into excess of aqueous sodium hydroxide. A very pale yellow solid was collected which separated from a large volume of alcohol or toluene in poorly-formed crystals, m. p. 247—249° (decomp.).

Other 2-guanidinoquinazolines were similarly prepared (Table). In the preparation of 6-methyl-2-guanidinoquinazoline, the evolved isobutene was dissolved in carbon disulphide and identified by its infrared spectrum.

1-(3-Guanidiniaminomethyl)decahydro-2,2,4-trimethylquinoline.—The base (10·9 g.) and dicyandiamide (4·2 g.) were boiled with a mixture of concentrated hydrochloric acid (5·2 ml.) and water (25 ml.) for 2 hr. After 2 days, large off-white prisms (7·3 g.), m. p. 192—194°, were filtered off. (A mixture with the hydrochloride, m. p. 193—210°, of the starting base had m. p. 160—170°.) Recrystallisation from ethanol gave the *hydrochloride* as prisms, m. p. 196—198° (Found: C, 56·6; H, 9·3; N, 23·0; Cl, 11·7. $C_{14}H_{28}ClN_5$ requires C, 55·7; H, 9·3; N, 23·2; Cl, 11·8%).

The free base was an oil.

4,6-Dimethyl-2-(4-methylquinazol-2-ylamino)pyrimidine (or Isomer).—2-Guanidino-4-methylquinazoline (12 g.) was powdered and boiled with acetylacetone (60 ml.) for 2 hr. The excess of diketone was distilled off under reduced pressure. The residue slowly solidified. Trituration

[12] Elliott and Dunathan, *Tetrahedron*, 1963, **19**, 833.

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Preparation of 2-guanidinoquinazolines from 1,2-dihydro-2,2-dimethylquinolines.

Other substituents	Yield (%)	M. p. of hydrochloride	M. p. of free base	Found (%) C	H	N	Cl	Formula of hydrochloride	Required (%) C	H	N	Cl	Notes
6-Me	29	316—317°	216—218°	50·2	5·5	26·8	13·8	$C_{10}H_{12}ClN_5$	50·5	5·1	29·9	14·5	*a*
4,6-Me_2	76	303—304 *	256—258	57·1	5·7			$C_{11}H_{14}ClN_5$	52·5	5·6			
4,7-Me_2	75	342		52·8	5·5	27·4	14·0	$C_{11}H_{14}ClN_5$	52·5	5·6	27·9	14·1	*b*
4,8-Me_2	58	249	265	61·3	6·0	32·3		$C_{11}H_{13}N_5$	61·4	6·0	32·6		*b, c*
6-Et, 4-Me	41	239—240	248—249	54·6	6·1			$C_{12}H_{16}ClN_5$	54·2	6·0			
6-Pr^i, 4-Me	31	233—234		56·0	6·8	24·9		$C_{13}H_{18}ClN_5$	55·8	6·4	25·0		
6-Bu, 4-Me	51	198—199	202—203			27·3		$C_{14}H_{19}N_5$			27·2		*c*
6-t-Bu, 4-Me	56	302—303 *	233—235	57·3	6·7			$C_{14}H_{20}ClN_5$	57·2	6·8			
6,6-CH_2, 4-Me	47	259—261	178—180	60·2	5·2			$C_{21}H_{22}N_{10}$	60·9	5·3			*c*
6-Cl, 4-Me	40	310		44·5	3·9	26·1	25·6	$C_{10}H_{11}Cl_2N_5$	44·1	4·0	25·7	26·1	
6-Br, 4-Me	43	293—295 *	263—264	38·1	3·7	23·7		$C_{10}H_{11}BrClN_5$	37·9	3·7	23·7		
6-MeO, 4-Me	68	326—328				26·2	13·3	$C_{11}H_{14}ClN_5O$			26·2	13·3	
6-EtO, 4-Me	77	268—269 *	263—264	50·6	5·9		12·2	$C_{12}H_{16}ClN_5O$	51·2	5·7		12·6	
8-EtO, 4-Me	47	301—302 *	219—221	51·1	5·6			$C_{12}H_{16}ClN_5O$	51·2	5·7			
6-Allyloxy, 4-Me	63	238—239		53·3	5·5	23·9	12·1	$C_{13}H_{16}ClN_5O$	53·2	5·5	23·8	12·1	
6-Hexyloxy, 4-Me	42	234—235	226—229	57·3	7·4	20·4		$C_{16}H_{24}ClN_5O$	56·9	7·1	20·7		
6-Decyloxy, 4-Me	52	181—182	204—205	60·7	8·4			$C_{20}H_{32}ClN_5O$	61·0	8·1			
6-Benzyloxy, 4-Me	21	273 *	206—207	59·6	5·4		10·1	$C_{17}H_{18}ClN_5O$	59·4	5·3		10·3	
7-Cl, 6-EtO, 4-Me	40	315 *		45·2	4·7			$C_{12}H_{15}Cl_2N_5O$	45·6	4·7			

* With decomposition.

(*a*) Consistently low figures for the nitrogen content of the hydrochloride were obtained. Found for the free base: N, 33·0. $C_{10}H_{11}N_5$ requires N, 34·8%. (*b*) With P. J. S. Bain. (*c*) Formula and analytical data are for the free base.

with ethanol yielded the above *compound* (11·2 g.) as an off-white solid, m. p. 134—135° (m. p. unaltered after recrystallisation from ethanol) (Found: C, 67·9; H, 5·9; N, 26·2. $C_{15}H_{15}N_5$ requires C, 67·9; H, 5·7; N, 26·4%).

The 6-*ethoxy-analogue*, similarly made from 6-ethoxy-2-guanidino-4-methylquinazoline (12 g.), separated from the reaction mixture in pale yellow plates (11 g.), m. p. 210—212° (m. p. 212—213° after recrystallisation from ethanol) (Found: C, 65·7; H, 6·2. $C_{17}H_{19}N_5O$ requires C, 66·0; H, 6·1%).

4-*Hydroxy*-6-*methyl*-2-(4-*methylquinazol*-2-*ylamino*)-*pyrimidine* (*or Isomer*).—A solution of 2-guanidino-4-methylquinazoline (4 g.) and ethyl acetoacetate (2·6 ml.) in 2-ethoxyethanol (50 ml.) was boiled for 30 min. Next day, buff plates (1·5 g.), m. p. 285—290°, were filtered off. The *compound* was amphoteric (Found: C, 62·6; H, 4·9. $C_{14}H_{13}N_5O$ requires C, 62·9; H, 4·9%).

2-*Amino*-4-*methylquinazoline*.—2-Guanidino-4-methylquinazoline (20 g.) was wetted with ethanol (50 ml.). A solution of sodium hydroxide (100 g.) in water (200 ml.) was then added. The mixture was heated and distillate (150 ml.) collected during *ca.* 90 min. This distillate contained 2-*amino*-4-*methylquinazoline* (1·9 g.). The bulk of this compound remained in the flask and was filtered off and recrystallised from water, forming long needles (7·3 g.), m. p. 154—159°. Recrystallisation from ethanol gave flocculent material which, when kept in contact with mother-liquor, slowly changed to large, off-white prisms, m. p. 156—159° (Found: C, 68·0; H, 5·7; N, 26·1. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%). This hydrolysis was also performed with sodium hydroxide in boiling ethylene glycol but the yield was somewhat less. The compound is fungistatic at 50 p.p.m.

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