s-Triazine is resistant to direct substitution[3]; furthermore its great sensitiveness to hydrolytic agents makes it only of limited value as a starting point into the triazine series. On the other hand, its unexpected reactivity might make it a useful tool in many other fields of organic synthesis.

Acknowledgment.—We are very much indebted to the Olin Mathieson Chemical Corporation for their generous support of this work.

Experimental[20]

General Procedure for the Preparation of N,N'-Disubstituted Formamidine and Heterocyclic Compounds.—The reaction can be carried out without any diluent or in a suitable solvent that does not itself react with *s*-triazine; for instance benzene, toluene, tetrahydrofuran, dioxane and dimethylformamide are recommended. Alcohols are suitable if strictly anhydrous.[21] Many amines, especially the lower aliphatic ones, react vigorously with *s*-triazine even at room temperature under evolution of ammonia; generally the reaction starts on warming the components up to about 80°. When working with higher-melting amines, the recommended procedure is to mix the amine intimately with *s*-triazine and to heat the mixture above the melting point of the amine. In such cases it is often more profitable to work in a solvent, especially if the amine or the expected reaction product is sensitive to heat. Working in an inert atmosphere, *e.g.*, nitrogen, was found necessary in the preparation of purine, in order to obtain the optimum yield. Generally 6 moles of the amine (or 3 moles of a diamine or any other bifunctional compound) are applied for one mole of *s*-triazine, but an excess of the latter never had a deleterious effect. A slight excess (about 10%) of *s*-triazine is recommended in cases where temperatures above 80° are necessary to start the reaction, as some triazine might escape the reaction owing to its high volatility. The reaction is usually finished when no more ammonia is evolved; if it is initially carried out below 100°, it is advisable to warm the mixture for 1 or 2 hours more to 100–120°, or to reflux it if working in a solvent. Working up presents no problem as no by-products except of ammonia are formed; an excess of *s*-triazine is easily removed, as it is far more volatile than any possible reaction product; it can also be destroyed by a short treatment of the reaction product with cold water.

COLUMBUS, OHIO

(20) All melting points are corrected; microanalyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(21) Our previous statement (THIS JOURNAL, **76**, 5648 (1954) that *s*-triazine undergoes solvolysis with alcohols is corrected thereby, the former results were obtained with the commercial "absolute" alcohol, which still contains 0.1–0.2% of water.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

1,2,3-Benzotriazines

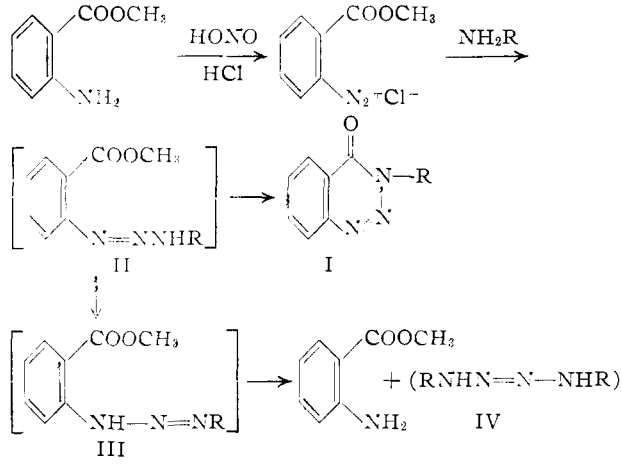
BY EARLE VAN HEYNINGEN

RECEIVED JULY 20, 1955

The synthesis of 3-substituted-3,4-dihydro-4-keto-1,2,3-benzotriazines from diazotized methyl anthranilate is reported.

There are recorded in the literature several methods for the synthesis of 3-substituted-3,4-dihydro-4-keto-1,2,3-benzotriazines. The usual technique has been to cyclize by diazotization an anthranilamide appropriately substituted on the amide nitrogen.[1] An alternative procedure was developed by Mehner[2] for 3-aryl derivatives in which an *o*-carbalkoxylphenylazoarylamine was ring closed in refluxing alcoholic solution. The only synthesis similar to the latter and not involving aryl amines was performed by Zacharias[3] in which an unsubstituted keto-1,2,3-benzotriazine resulted directly from the neutralization of diazotized ethyl anthranilate with ammonium hydroxide.

The latter reaction has now been examined for the extent of its application. It was thought probable that neutralization of diazotized methyl anthranilate with aliphatic amines would give the 3-substituted 4-keto-1,2,3-benzotriazines. This was found to be the case and compounds corresponding to I were obtained in moderate yields with simple aliphatic amines. Primary aliphatic amines with hydroxyl, secondary amino or carboxylate groups substituted on the alkyl group generally furnished the expected products in good yields.



In two cases side reactions predominated over the cyclization. When ethylamine was used, methyl anthranilate was isolated in nearly 60% yield along with a small amount of the anticipated 3-ethyl-3,4-dihydro-4-keto-1,2,3-benzotriazine. This same phenomenon accompanied the formation of a bis-ketobenzotriazinylethylene from ethylenediamine. Evidently, in these reactions the intermediate II tautomerizes to an intermediate such as III and the latter is cleaved by excess amine to methyl anthranilate. The other product of such a cleavage is conjectured to be IV, but no positive evidence was obtained for its existence or that of any of its possible decomposition products.

(1) A. Weddige and H. Finger, *J. prakt. Chem.*, [2] **35**, 263 (1887); H. Finger, *ibid.*, [2] **37**, 435 (1888); **48**, 92 (1893); A. Pictet and A. Gonset, *Chem. Zentr.*, **68**, I, 413 (1897); H. Meyer, *Ann.*, **351**, 278 (1907); K. Kratz, *J. prakt. Chem.*, [2] **53**, 213 (1896); H, King and W. O. Murch, *J. Chem. Soc.*, **125**, 2595 (1924).

(2) H. Mehner, *J. prakt. Chem.*, [2] **63**, 266 (1901).

(3) E. Zacharias, *ibid.*, [2] **43**, 446 (1881).

TABLE I

3R-3,4-DIHYDRO-4-KETO-1,2,3-BENZOTRIAZINES

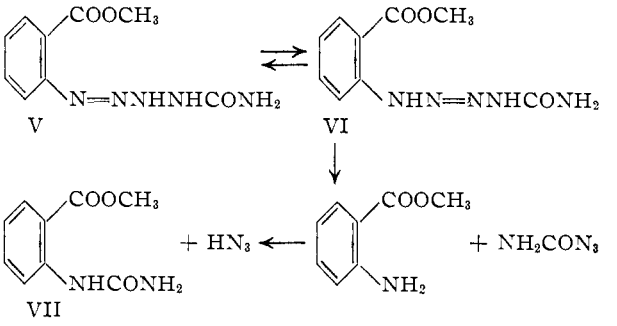
R	Yield, %	B.p., °C.	Mm.	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	27			120–122[a]	$C_8H_7N_3O$	59.62	59.81	4.38	4.29
C_2H_5	17			70–71[b]	$C_9H_9N_3O$	61.70	61.97	5.17	5.53
$CH_2{=}CHCH_2$	50	105	1.1		$C_{10}H_9N_3O$	64.16	64.63	4.85	5.07
$HOCH_2CH_2$	39.5			116–118[c]	$C_9H_9N_3O_2$	56.54	56.49	4.64	4.62
$(HOCH_2)_2CH$	16.5	117–120	3.3		$C_{10}H_{11}N_3O_3$	54.29	54.31	5.01	5.14
$(CH_3)_2NCH_2CH_2$	56			61–62[b]	$C_{11}H_{14}N_4O$	60.53	60.61	6.47	6.52
$(CH_3)_2NCH_2CH_2\cdot HCl$				222–224[d]	$C_{11}H_{15}ClN_4O$	51.86	51.65	5.94	5.83
$(C_2H_5)_2NCH_2CH_2$	65	176	1.6		$C_{13}H_{18}N_4O$	63.39	63.33	7.37	7.51
$(C_2H_5)_2NCH_2CH_2\cdot HCl$				226 dec.[d]	$C_{13}H_{19}ClN_4O$	55.21	55.44	6.77	6.76
$(CH_3)_2N(CH_2)_3$	78	178	2.4		$C_{12}H_{16}N_4O$	62.05	61.90	6.95	6.84
$(CH_3)_2N(CH_2)_3\cdot HCl$				208–210 d.[d]	$C_{12}H_{17}ClN_4O$	53.63	53.42	6.38	6.53
$O[(CH_2)_2]_2NCH_2CH_2$	70			99[a]	$C_{13}H_{18}N_4O_2$	59.98	60.09	6.20	6.43
$O[(CH_2)_2]_2NCH_2CH_2\cdot HCl$				230–232[e]	$C_{13}H_{19}ClN_4O_2$	52.61	52.84	5.78	5.97
$(C_2H_5)_2N(CH_2)_3CH(CH_3)$	53	185	1.1		$C_{16}H_{24}N_4O$	66.63	66.40	8.39	8.16
$(C_2H_5)_2N(CH_2)_3CH(CH_3)\cdot HCl$				130–131[d]	$C_{16}H_{25}ClN_4O$	59.15	59.03	7.76	7.47
$(CH_2)_2$	11			213–215[a]	$C_{16}H_{12}N_6O_2$	59.99	60.09	3.78	3.91
$C_2H_5O_2CCH_2$	17.5			98–100[a]	$C_{11}H_{11}N_3O_3$	56.65	56.68	4.76	4.98
$HOOCCH_2$	45			193–194	$C_9H_7N_3O_3$	52.68	52.74	3.44	3.57

[a] Benzene–petroleum ether (60–64°). [b] Petroleum ether (60–64°). [c] Benzene. [d] Ethanol–ether. [e] Methanol–ether.

Examination of the yields of products in Table I reveals that aliphatic diamines generally form the benzotriazines in better yields than aliphatic monamines, suggesting that the tertiary amine group is of aid in the cyclization. This also suggests that the customary two-step reaction, coupling and then cyclization to 3-aryl compounds, might be one-step when primary amines of heterocyclic bases are used; the presence of the tertiary amine group might induce cyclization *in situ*. However, 2-aminopyridine and 3-aminoquinoline yielded diazoamines in the coupling reaction and cyclization occurred only when the latter were refluxed with alcoholic sodium alkoxide.

When the preparation of a hydrochloride of the 3α-pyridyl derivative of I was attempted, there was isolated the hydrochloride of 2-benzamidopyridine instead. A possible explanation of its formation is that excess hydrogen chloride reacted with the benzotriazine to form the diazonium chloride which was reduced to the observed product by the boiling methanol used to recrystallize it.

An attempt to make 3-amino and substituted 3-amino derivatives of I in a similar fashion to the 3-alkyl compounds proved unsuccessful. A 3-anilino derivative has been made by diazotizing and so ring closing anthranilyl hydrazide.[4] When diazotized methyl anthranilate was treated with excess hydrazine the products were methyl anthranilate and *o*-carbomethoxyphenylazide. With the thought that a properly substituted hydrazine might enter into the cyclization reaction, semicarbazide was employed. The sole product isolated from this reaction proved to be a methyl *o*-ureidobenzoate (VII). Curtius[5] already has showed that treatment of diazonium salts with hydrazine and its derivatives leads to azides and amines. Evidently the diazoamino compounds from hydrazine and its derivatives decompose at a faster rate than the cyclization to benzotriazines can occur. The isolation of VII does not at first seem explainable on the basis of Curtius' results. However, if the cleavage of the coupling product occurred in the customary fashion to give methyl anthranilate and carbamyl azide, the latter could then acylate the methyl anthranilate to give the methyl *o*-ureidobenzoate (VII).



Experimental[6]

General Procedure for the Preparation of 3-Alkyl or Substituted Alkyl-3,4-dihydro-4-keto-1,2,3-benzotriazines (I).—Methyl anthranilate was dissolved in three equivalents of dilute hydrochloric acid and ice and diazotized to a starch–iodide end-point. An aliquot of approximately 300–400 ml. containing one-third mole of the diazonium salt was then cooled in ice and a one- to twofold molar excess of the amine was added from a dropping funnel into the stirred solution. In those instances where diamines were used one-third molar excess was employed. With each drop a precipitate generally separated which resulted in either an oily layer or a frothy solid. Stirring was continued for one hour and the product filtered if solid or extracted with ether if liquid. The solids were washed with water and then air-dried. They were recrystallized from the appropriate solvents to constant melting point. The liquids in ether were dried with magnesium sulfate, the ether was removed, and the products were distilled under reduced pressure to give in general viscous oils of yellow cast.

The hydrochlorides of the products with amine substituents were prepared by bubbling dry hydrogen chloride through ether solutions of the compounds, separating the

(4) A. Konig and A. Reissert, *Ber.*, **32**, 783 (1899).

(5) Th. Curtius, *ibid.*, **26**, 1261 (1893).

(6) All melting points and boiling points are uncorrected. The analyses were performed by H. L. Hunter, G. M. Maciak and W. Schenck.

precipitated hydrochloride by filtration, and recrystallizing by solution in ethanol and addition of ether.

Preparation of 3-Ethyl-3,4-dihydro-4-keto-1,2,3-benzotriazine.—The reaction was run in the manner described above using 0.333 mole of diazotized methyl anthranilate and 0.8 mole of ethylamine in 35% aqueous solution. The oil produced by this reaction was distilled at 0.9 mm. A first fraction boiled mainly at 115°, $n^{25}D$ 1.5815. It was obtained in a 29.5-g. yield. On analysis this fraction was showed to be methyl anthranilate ($n^{20}D$ 1.5844).

Anal. Calcd. for $C_8H_9NO_2$: C, 63.57; H, 6.00. Found: C, 63.38; H, 6.12.

A higher boiling fraction, 120° (0.9 mm.), was also obtained which crystallized on standing. It was recrystallized from 60–64° petroleum ether, m.p. 69–70°. Analysis (see Table I) proved it to be the desired product.

Preparation of Bis-3-(3,4-dihydro-4-keto-1,2,3-benzotriazinyl)-ethylene.—The general procedure was employed using 0.4 mole of ethylenediamine to 0.333 mole of diazonium chloride. A solid was obtained (24.0 g.) which was recrystallized several times from benzene–petroleum ether to give 6.0 g. of a substance with m.p. 213–215°. Analysis proved it to be the disubstituted ethylene. The filtrates from the purification were evaporated to dryness; the residue was dissolved in dry ether and an hydrochloride was made by passing in dry hydrogen chloride, m.p. 180–181°. Analysis, melting point and mixed-melting point with authentic methyl anthranilate hydrochloride proved the identity of this material.

Anal. Calcd. for $C_8H_{10}ClNO_2$: C, 51.20; H, 5.37. Found: C, 50.87; H, 5.48.

Preparation of 2-(*p*-Carbomethoxyphenyldiazoamino)-pyridine.—The coupling was performed between 0.4 mole of 2-aminopyridine and 0.333 mole of diazotized methyl anthranilate. After the two were mixed 35 g. of hydrated sodium acetate was added. The precipitate was filtered and dried in air to give 54.0 g. of crude azoamine. Recrystallized from methanol it melted at 119–121°.

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72. Found: C, 60.70; H, 4.94.

Preparation of 3-(2-Pyridyl)-3,4-dihydro-4-keto-1,2,3-benzotriazine.—In a 500-ml. flask sodium ethoxide was made from 2.3 g. (0.1 atom) of sodium in 200 ml. of dry ethanol. Then 25.0 g. (0.102 mole) of 2-(*o*-carbomethoxyphenylazoamino)-pyridine was added and the mixture refluxed for an hour. The reaction mixture was cooled and filtered. The yellow product was recrystallized from methanol, m.p. 189–190°; yield 16.0 g. (0.071 mole), 70%.

Anal. Calcd. for $C_{12}H_8N_4O$: C, 64.28; H, 3.60. Found: C, 64.04; H, 3.71.

A solid hydrochloride was prepared from an ether solution of the product and recrystallized from hot methanol by the addition of ether. A substance was obtained, m.p. 187–190°, with an analysis that checked for 2-benzamidopyridine hydrochloride.

Anal. Calcd. for $C_{12}H_{11}ClN_2O$: C, 61.41; H, 4.73; N, 11.94. Found: C, 60.95; H, 5.00; N, 11.65.

A sample on neutralization with ammonium hydroxide gave a compound, m.p. 76–78°. A picrate melted at 192–194°, agreeing with literature values for 2-benzamidopyridine.[7]

Preparation of 3-(*o*-Carbomethoxyphenylazoamino)-quinoline.—This preparation was performed as above for the pyridine compound. There was thus obtained from 0.35 mole of 3-aminoquinoline hydrochloride a hydrophilic solid which after drying was recrystallized several times from methanol; m.p. 128–130°, yellow micro-crystals, 39.5 g. (0.144 mole), 43% yield.

Anal. Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.65; H, 4.61; N, 18.29. Found: C, 66.46; H, 5.17; N, 18.09.

Preparation of 3-(3-Quinolyl)-3,4-dihydro-4-keto-1,2,3-benzotriazine.—The azoamine was cyclized in refluxing methanol with a sodium methoxide catalyst. So from the reaction of 0.05 mole of azoamine with 0.01 atom of sodium methoxide, there was isolated a product which was recrystallized from a large volume of methanol three times, treating with charcoal once. It was obtained as feathery, white needles, m.p. 188–189° with prior softening, yield 1.0 g.

Anal. Calcd. for $C_{16}H_{10}N_4O$: C, 70.06; H, 3.68. Found: C, 69.79; H, 3.67.

Attempted Preparation of 3-Amino Derivatives. a. The Reaction with Hydrazine.—Methyl anthranilate (0.2 mole) was diazotized and then cooled while 35 g. (0.7 mole) of hydrazine hydrate was added slowly. After complete addition the solution was extracted with ether. Evaporation of the ether gave a mobile oil, 27.6 g. It was redissolved in ether and extracted with 75 ml. of hydrochloric acid. The ether solution was evaporated and the residue was distilled to give *o*-carbomethoxyphenylazide, b.p. 114° (1.9 mm.), $n^{25}D$ 1.5722, in 20-g. yield, 56.5%. The water solution was basified with sodium carbonate, extracted with ether and the latter dried. Passing hydrogen chloride through this solution gave 6 g. of methyl anthranilate hydrochloride, m.p. 180° (16%).

b. The Reaction with Semicarbazide.—In a sodium acetate buffered solution diazotized methyl anthranilate (0.248 mole) was treated with semicarbazide hydrochloride (0.248 mole). A sticky, fluffy solid separated which was filtered as dry as possible and then allowed to stand overnight. It had in this time separated into oily crystals and water. The crystals were filtered and recrystallized repeatedly from benzene, m.p. 173–176° with softening, 3.5 g. Analysis and comparison with an authentic sample[8] proved it to be methyl *o*-ureidobenzoate.

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.69; H, 5.19; N, 14.44. Found: C, 55.70; H, 5.33; N, 14.44.

Preparation of 3-Carboxymethyl-3,4-dihydro-4-keto-1,2,3-benzotriazine.—The corresponding ethyl ester (see Table) was saponified by mixing 6 g. (0.025 mole) with a solution of 1.0 g. (0.025 mole) of sodium hydroxide in 25 ml. of water and 100 ml. of methanol and refluxing 1.5 hours. The product was isolated by evaporation to dryness, solution of the residue in water, acidification and filtration after cooling. Recrystallized from water, it melted at 193–194°, yield 2.3 g. (0.012 mole), 45%.

INDIANAPOLIS, INDIANA

(7) A. E. Tschitschibabin and J. G. Bylinken, *Ber.*, **55**, 998 (1922).

(8) M. T. Bogert and G. Scatchard, THIS JOURNAL, **41**, 2056 (1919).