Diethyl malonate as leaving group: Facile synthesis of some 1,3,4-benzotriazepines and benzotriazepinones

C. Podesva, G. Kohan, and K. Vagi
Delmar Chemicals Limited, Lasalle, Quebec

Received August 16, 1968

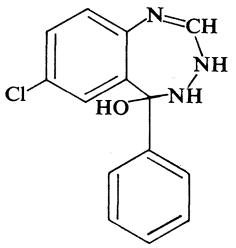
Reaction between 2-(2′,2′-bis-carboethoxyvinylamino)-benzophenones, resulting from the condensation of 2-aminobenzophenones with diethyl ethoxymethylenemalonate, and hydrazine hydrate yields 5-hydroxy-5-phenyl-1,3,4-3*H*-4,5-dihydrobenzotriazepines or their double bond isomers. These products on acetylation afford *O*,*N*,*N*-triacetates, which on treatment with ammonia are transformed into 4-phenylquinazolines. Structure proof of these substances is reported.

Canadian Journal of Chemistry, **47**, 489 (1969)

When diethyl ethoxymethylenemalonate was heated together with 2-amino-5-chlorobenzophenone, the expected 2-(2′,2′-bis-carboethoxyvinylamino)-5-chlorobenzophenone (**1**) was readily formed. Other 2-aminobenzophenones as well as methyl anthranilate and methyl 5-chloroanthranilate reacted in the same manner. The infrared (i.r.) spectra of these substances were in good agreement with the assigned structures, exhibiting α,β-unsaturated ester absorptions at 1680 cm^{-1} together with the benzophenone carbonyl absorption at 1640 cm^{-1}. The reaction products are summarized in Table I.

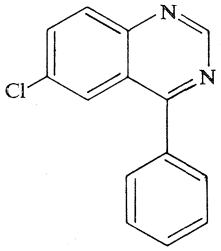
When **1** was allowed to react with hydrazine hydrate in methanolic solution at room temperature, a high yield of a crystalline material could be isolated whose elemental analysis corresponded to a formula of $C_{14}H_{12}Cl\ N_3O$. Obviously, this substance must have been formed from the starting material by the elimination of the diethyl malonate moiety and by the addition of one molecule of hydrazine. Its i.r. spectra (KBr) exhibited a sharp peak at 3325 cm^{-1}, a peak of medium intensity at 2780 cm^{-1} together with a weaker peak at 2600 cm^{-1}, thus disclosing very strong hydrogen bonding (1, 2), plus a strong peak at 1640 cm^{-1}. On acetylation of this product with acetic anhydride in pyridine an *O*,*N*,*N*-triacetate was formed (ν_{max} (KBr) 1730, 1665, and 1645 cm^{-1}), which on controlled alkaline hydrolysis afforded an *N*,*N*-diacetate having a free hydroxyl (ν_{max} (KBr) 3230, 1670, and 1620 cm^{-1}). In the light of this, the i.r. absorption at 1640 cm^{-1} in the original product must be assigned to a C=N grouping rather than a C=O.

From the presence of the C=N and OH together with three N atoms in the molecule and in view of the nature of starting material it was concluded that the initial product had to possess a 1,3,4-benzotriazepine skeleton. The hydroxyl group could be attached either to C-5 and the position of the double bond then would be as shown in structure **7** or between C-2 and N-3, or to C-2 with the double bond between N-4 and C-5.

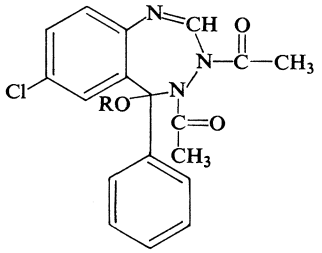


7

The position of attachment of the hydroxyl was established in a somewhat unexpected way. On attempted selective saponification of the ester function in the above mentioned *O*,*N*,*N*-triacetate with aqueous methanolic ammonia, a high yield of a crystalline substance was isolated which was identified as 4-phenyl-6-chloroquinazoline (**8**) by comparison of physical properties and i.r. spectra



8

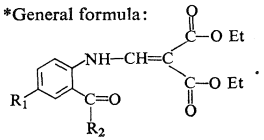


9, R = Ac
10, R = H

TABLE I

Compound*	R_1	R_2	Yield, %	Melting point (°C)	Solvent†	Formula	C (%) Calcd.	C (%) Found	H (%) Calcd.	H (%) Found	N (%) Calcd.	N (%) Found
1	Cl	Ph	77	135–137	*a*	$C_{21}H_{20}ClNO_5$‡	62.76	62.72	5.01	4.75	3.48	3.82
2	H	Ph	72	105–107	*b*	$C_{21}H_{21}NO_5$	68.65	68.75	5.76	5.67	3.81	4.03
3	Cl	2-Cl Ph	50	180–182	*a*	$C_{21}H_{19}Cl_2NO_5$§	57.81	58.03	4.38	4.53	3.20	3.43
4	NO_2	Ph	92	172–174	*a*	$C_{21}H_{20}N_2O_7$	61.15	61.07	4.88	4.87	6.79	7.05
5	H	OCH_3	78	71–72	*c*	$C_{16}H_{19}NO_6$	59.80	59.70	5.96	6.30	4.36	4.11
6	Cl	OCH_3	83	95	*d*	$C_{16}H_{18}ClNO_6$‖	54.01	54.26	5.10	5.22	3.94	3.82

*General formula:



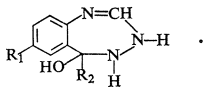
†Solvents: *a*, methanol; *b*, ethanol; *c*, hexane; *d*, aqueous methanol.
‡Anal. Calcd.: Cl, 8.82; Found: Cl, 8.79.
§Anal. Calcd.: Cl, 16.25; Found: Cl, 16.37.
‖Anal. Calcd.: Cl, 9.97; Found: Cl, 10.17.

TABLE II

5-Hydroxy-5-phenyl-1,3,4-3*H*-4,5-dihydrobenzotriazepines*

Compound	R_1	R_2	Yield, %	Melting point (°C)	Solvent†	Formula	C (%) Calcd.	C (%) Found	H (%) Calcd.	H (%) Found	N (%) Calcd.	N (%) Found
7	Cl	Ph	90	198–200‖	*a*	$C_{14}H_{12}ClN_3O$‡	61.43	61.59	4.42	4.73	15.34	15.24
11	H	Ph	88	179–181	*b*	$C_{14}H_{13}N_3O$	70.27	69.99	5.47	5.60	17.50	17.82
12	Cl	2-Cl Ph	75	200	*a*	$C_{14}H_{11}Cl_2N_3O$§	54.56	54.94	3.59	3.88	13.63	13.88
13	NO_2	Ph	86	190–191	*b*	$C_{14}H_{12}N_4O_3$	59.14	59.29	4.25	4.40	19.71	19.96

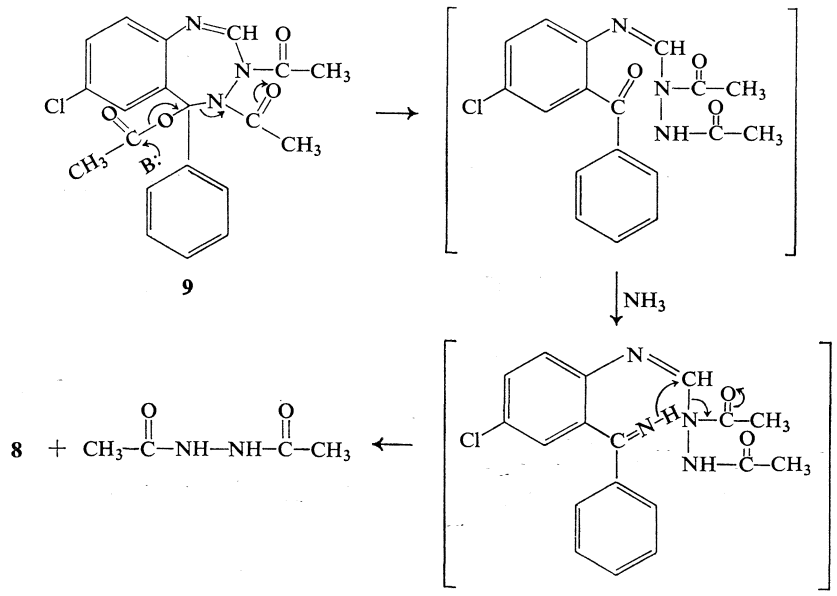
*General formula:



†Solvents: *a*, dimethyl formamide – water; *b*, methanol.
‡Anal. Calcd.: Cl, 12.95; Found: Cl, 13.16.
§Anal. Calcd.: Cl, 23.03; Found: Cl, 23.33.
‖Sometimes a different crystalline form having a m.p. of 185–187°, but having the same i.r. spectrum was obtained.

with a sample prepared by an independent synthesis.

The same product was also obtained when the diester **1** was subjected to a similar treatment using methanolic ammonia, and also when the *N,N*-diacetate was kept for some time in aqueous methanolic ammonia solution in presence of catalytic amount of triethylamine. (It is noteworthy, that whereas in the case of the triacetate the reaction was completed in about 30 min, the uncatalyzed reaction with the *N,N*-diacetate proceeded very slowly. A likely explanation is, that in the first case the liberated electron pair on the alcoholic oxygen immediately became involved in the transfer shown in the postulated mechanism (*vide infra*), whereas once protonated a stronger base than ammonia was needed to produce the necessary anion). On the other hand, when the non-acetylated material was treated with aqueous methanolic ammonia under the same conditions, the starting material was recovered unchanged, thus showing that in order for elimination to occur the hydrazine portion had to be acetylated. A plausible mechanism for the formation of **8** from the triacetate formulated as **9** can be represented as follows:

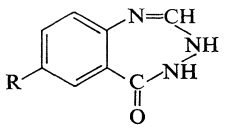


9

It can be seen, that the above mechanism postulates elimination of hydrazine in the form of a symmetrical diacetate. On the other hand, if a similar elimination is considered for the diacetylated 2-hydroxy isomer, an unlikely ammonolysis of an *N*-acetyl would be anticipated and hydrazine would have to be eliminated in the form of a monoacetate. As we were able, however, to isolate from the reaction mother liquors a high yield of 1,2-diacetylhydrazine, identified by comparison of its physical properties and i.r. spectra with a sample prepared by an independent synthesis, the correctness of the above mechanism is rigorously proved and at the same time the sites of the acetylation as well as the position of the double bond in the acetates clearly established, as shown in structures **9** and **10**. Consequently, for the nonacetylated product, structure **7** would appear to be the most likely one. As, however, a double bond migration might have taken place during the acetylation, a double bond isomer of **7** cannot be excluded. Attempts to solve this question by nuclear magnetic resonance (n.m.r.) spectra were frustrated by insufficient solubility of this substance in deuterated solvents.

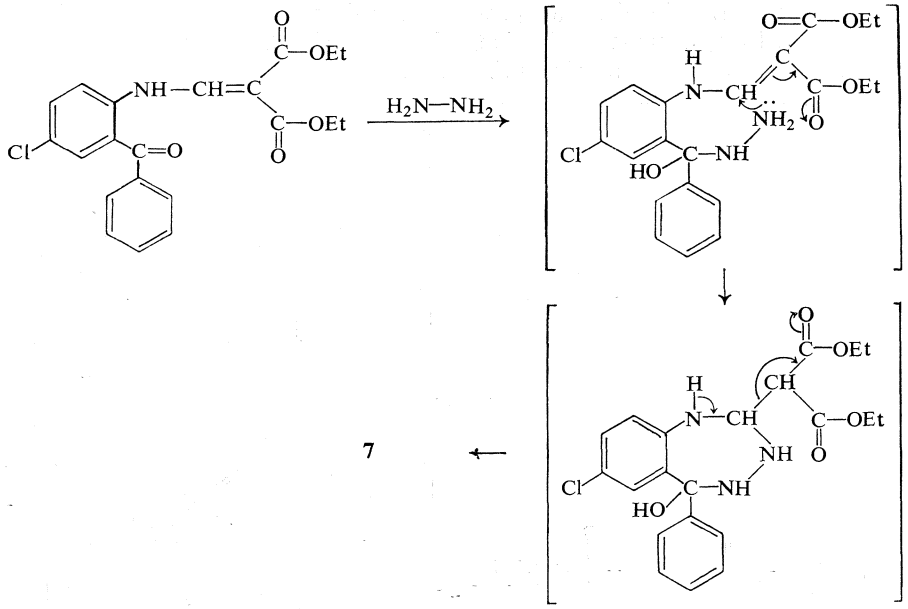
When compounds **2**–**4** listed in Table I, were brought in contact with hydrazine hydrate under the same conditions as **1**, they afforded readily the corresponding 1,3,4-benzotriazepines listed in Table II. Similarly compounds **5** and **6**, when allowed to react with hydrazine hydrate, yielded the corresponding 1,3,4-benzotriazepine-5-ones

14 and **15**. (We placed the double bonds in **14** and **15** between N-1 and C-2 by analogy with the benzotriazepines listed in Table II, nevertheless, we do not have any rigorous proof for this assignment. Ultraviolet spectra proved to be of little value due to the lack of appropriate models).



14, R = H
15, R = Cl

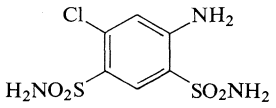
The reaction mechanism by which 1,3,4-3*H*-4,5-dihydrobenzotriazepines are formed from the appropriate 2-(2′,2′-bis-carbethoxyvinylamino)-benzophenones and hydrazine hydrate is readily conceivable and can be represented as follows:



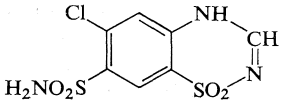
7

Because the above reactions were carried out using an excess of hydrazine hydrate, the question arose as to whether the leaving group is indeed diethyl malonate or rather pyrazolidine-3,5-dione resulting from the hydrazinolysis of the diester. For that reason the reaction was repeated using only one mole equivalent of hydrazine hydrate. Isolation of about the same yield of the benzotriazepine as in the previous experiments clearly showed that the leaving group is indeed the diethyl malonate.

The general applicability of the above described method for introduction of a =CH— group between two nitrogens was further tested by treating 1-amino-3-chlorobenzene-4,6-disulfonamide **16** with diethylethoxymethylenemalonate. The expected 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide **17**, identified by comparison of physical properties and i.r. spectra with an authentic sample prepared by independent synthesis was obtained in high yield. The above described method has therefore a wide applicability and constitutes a method of choice whenever the use of formic acid, ethyl orthoformate etc. is excluded for one reason or other.



16



17

Experimental

The i.r. spectra were taken on Perkin–Elmer 237 and 237B instruments. The melting points were determined in capillaries on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Dr. C. Daessle, Organic Microanalysis, Montreal.

Condensation of Diethyl Ethoxymethylenemalonate with 2-Aminobenzophenones and Anthranilic Esters

General Procedure

A mixture of approximately equal weights of the appropriate amine and diethyl ethoxymethylenemalonate was kept at a temperature of about 110° (140° in case of anthranilic esters) for 30 min. After cooling to about 80° the reaction mixture was diluted with some ethanol and the reaction product was allowed to crystallize in an ice box overnight. The crystalline material was collected by filtration and recrystallized from the appropriate solvent.

Synthesis of 5-Hydroxy-5-phenyl-1,3,4-3H-4,5-dihydrobenzotriazepines

General Procedure

An approximately 10% ethanolic solution of the diester was stirred at room temperature overnight in presence of 1–3 mole equivalents of hydrazine hydrate. The crystalline reaction product was collected by filtration, washed with water, and recrystallized from the appropriate solvent.

*1,3,4-3H-4,5-Dihydrobenzotriazepine-5-one (**14**)*

A solution of **5** (2 g) in ethanol (10 ml) was left standing at room temperature for 4 days in presence of 100% hydrazine hydrate (1 g). The crystalline precipitate was collected by filtration, washed with some ethanol (0.94 g, 94%), and recrystallized for analysis from isopropanol, m.p. 214–215°.

Anal. Calcd. for $C_8H_7N_3O$: C, 59.61; H, 4.38; N, 26.07. Found: C, 59.74; H, 4.51; N, 25.84.

*7-Chloro-1,3,4-3H-4,5-dihydrobenzotriazepine-5-one (**15**)*

A solution of **6** (7.1 g) in ethanol (50 ml) containing 100% hydrazine hydrate (3 g) was allowed to stand at room temperature for overnight. The crystalline precipitate was collected by filtration (3 g, 77%), washed with some ethanol, and recrystallized for analysis from chloroform – methanol mixture, m.p. 230–232°.

Anal. Calcd. for $C_8H_6Cl\ N_3O$: C, 49.11; H, 3.09; Cl, 18.13; N, 21.48. Found: C, 49.00; H, 2.84; Cl, 18.31; N, 21.43.

*Acetylation of **7***

A mixture of **7** (54.7 g, 0.2 mole), acetic anhydride (122.4 g, 1.2 mole), and dry pyridine (170 ml) was allowed to stand at room temperature for 48 h. The reaction mixture was evaporated to dryness *in vacuo* and water was added to the residue. The reaction product was extracted into 2 × 150 ml of chloroform and the solution washed first with 5% HCl, then with 15% aqueous solution of $NaHCO_3$, and eventually with water. The solvent was removed *in vacuo* and the residue crystallized first from ethanol, then from methanol. The yield of **9** was 42 g (52.5%), m.p. 103–104°.

Anal. Calcd. for $C_{20}H_{18}Cl\ N_3O_4$: C, 60.07; H, 4.53; Cl, 8.86; N, 10.50. Found: C, 60.15; H, 4.72; Cl, 9.05; N, 10.68.

*Saponification of **9***

To a solution of **9** (8 g, 0.02 mole) in methanol (20 ml), previously warmed to about 45°, was added alcoholic KOH till a pH of about 10 was reached. After allowing the warm solution to stand for about 30 min, cold water (300 ml) was added; the precipitated solid was collected by filtration, washed with water, and dried at 60° (6 g, 85.7%). The analytically pure **10**, m.p. 170–172°, was prepared by crystallization from tetrahydrofuran – ether mixture.

Anal. Calcd. for $C_{18}H_{16}Cl\ N_3O_3$: C, 60.42; H, 4.51; Cl, 9.91; N, 11.74. Found: C, 60.61; H, 4.55; Cl, 10.07; N, 11.91.

*4-Phenyl-6-chloroquinazoline (**8**)*

Method a

To a solution of **9** (18 g, 0.0045 mole) in methanol (50 ml) was added aqueous NH_3 till a pH of 9.5 was reached. After standing for 30 min at a temperature of about 30°, the reaction mixture was cooled to 0° and the precipitated **8** (9.72 g, 90%) was collected by filtration and purified by crystallization from methanol, m.p. 137–139°.

Anal. Calcd. for $C_{14}H_9Cl\ N_2$: C, 69.89; H, 3.77; Cl, 14.74; N, 11.64. Found: C, 70.10; H, 3.94; Cl, 15.04; N, 11.59.

This product was found identical by comparison of physical properties and i.r. spectra with the product obtained by a method described by Palazzo for the preparation of 4-phenylquinazoline (3), using 2-amino-5-chlorobenzophenone instead of 2-aminobenzophenone. The filtrate from the above experiment was evaporated to dryness *in vacuo* and the residue (4 g, 80%) was recrystallized from methanol, m.p. 138–139°. It was found identical with 1,2-diacetylhydrazine prepared by the method of Stollé (4), by comparison of physical properties and i.r. spectra.

Method b

A solution of **1** (2 g, 0.005 mole) in anhydrous methanol (150 ml) previously cooled in an ice bath was saturated with NH_3 gas. After standing at room temperature over the weekend, the reaction mixture was concentrated to a small volume under reduced pressure and the crystalline precipitate was collected by filtration (0.6 g, 50%) and recrystallized from methanol, m.p. 137–139°, undepressed on admixture of the product obtained by Method *a*. Infrared spectra of these two products were superimposable.

Method c

A solution of **10** (0.7 g, 0.00195 mole) in a mixture of methanol (70 ml) and water (20 ml) containing a few drops of triethylamine was saturated with HN_3 gas and allowed to stand at room temperature overnight. The reaction mixture was concentrated to a small volume under reduced pressure, diluted with water, and the reaction product was extracted into chloroform. The solution was evaporated to dryness *in vacuo* and the residue treated with a small amount of methanol. The crystalline reaction product was collected by filtration (0.15 g, 31%) and identified as **8** by m.p., mixture m.p., and by comparison of i.r. spectra.

When the above experiment was carried out in absence of triethylamine, most of the starting material was recovered even after 48 h standing.

*6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (**17**)*

A mixture of **16** (5.4 g, 0.02 mole) and diethyl ethoxymethylenemalonate (4.32 g, 0.02 mole) was heated to 210° for 10 min. After cooling the solid product was triturated with methanol, collected by filtration, and purified by recrystallization from methanol – ethyl acetate mixture. The yield was 3 g (51%), m.p. 343°, undepressed

on admixture of a sample prepared by a previously described method (5). The i.r. spectra of these two products were superimposable.

Acknowledgments

Skillful technical assistance was provided by Miss Anna Nagy and Mr. Peter Pipasts.

1. A. FOLDES and C. SANDORFY. J. Mol. Spectry. **20**, 262 (1966).
2. H. ZIMMERMAN. Z. Elektrochem. **65**, 821 (1961).
3. S. PALAZZO. Boll. sedute accad. Gioenia sci. nat. Catania, **71**, No. 227, 75 (1959); Chem. Abstr. **55**, 12412*i* (1961).
4. R. STOLLÉ. Ber. **32**, 796 (1899).
5. F. C. NOVELLO. U. S. Patent No. 2,809,194 to Merck and Co., Inc., Rahway, New Jersey. (1957).

This article has been cited by:

1. Ibrahim Chaaban, El Sayeda M. El Khawass, Mona A. Mahran, Heba A. Abd El Razik, Nehad S. El Salamouni. 2012. Unexpected products from the reaction of different compounds with hydrazine hydrate or aryl thiosemicarbazides. *Journal of Saudi Chemical Society* . [CrossRef]
2. Bassam A. Abu Thaher, Jalal A. Zahra, Mustafa M. El-Abadelah. 2002. Facile synthesis of model 1,4-dihydro-1 H -1,3,4-benzotriazepin-5-ones. *Journal of Heterocyclic Chemistry* **39**:10.1002/jhet.v39:5, 901-904. [CrossRef]
3. Ping Lue, John V. GreenhillEnaminones in Heterocyclic Synthesis 207-343. [CrossRef]
4. References 379-428. [CrossRef]
5. Robert W. Leiby. 1984. The chemistry of 2-aminobenzoyl hydrazides. 1. Effects of orthoester substituents on the mode of cyclization. *Journal of Heterocyclic Chemistry* **21**:10.1002/jhet.v21:6, 1825-1832. [CrossRef]
6. Peter Scheiner, Leroy Frank, Irene Giusti, Sara Arwin, Shirley A. Pearson, Frendy Excellent, Althea P. Harper. 1984. 1,3,4-Benzotriazepinones. Formation and rearrangement. *Journal of Heterocyclic Chemistry* **21**:10.1002/jhet.v21:6, 1817-1824. [CrossRef]
7. J. Y. Mérour. 1982. Synthèse spécifique de pyrimidines. Formation conccurentielle de pyrimidines et de triazépines. *Journal of Heterocyclic Chemistry* **19**:10.1002/jhet.v19:6, 1425-1431. [CrossRef]
8. Charles F. Beam, Charles A. Park, Ned D. Heindel, William P. Fives. 1977. The Synthesis of 2-Carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-4(1 H)quinazolinones. *Journal of Heterocyclic Chemistry* **14**:10.1002/jhet.v14:4, 703-704. [CrossRef]
9. Milton J. Kornet. 1973. Reaction of methyl 2-[2′,2′-bis(carbethoxy)vinylamino]benzoate with hydrazine. *Journal of Pharmaceutical Sciences* **62**:10.1002/jps.v62:5, 834-835. [CrossRef]
10. I.K. Kim, K.L. Erickson. 1971. Models for uleine-alkaloid biogenesis. *Tetrahedron* **27**, 3979-3991. [CrossRef]
11. M.E. Derieg, J.F. Blount, R.Ian Fryer, S.S. Hillery. 1970. 3-Aminoquinazolines: Structural assignments. *Tetrahedron Letters* **11**, 3869-3872. [CrossRef]
12. A.T. Balaban. 1970. Reaction of pyrylium salts with nucleophiles—IX. *Tetrahedron* **26**, 739-742. [CrossRef]