Reaction of Methyl 2-[2′,2′-Bis(carbethoxy)vinylamino]benzoate with Hydrazine

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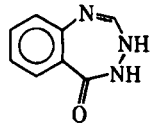
Abstract □ Previous workers incorrectly assigned the 1,3,4-benzotriazepine-5-one structure to the product resulting from the reaction of methyl 2-[2′,2′-bis(carbethoxy)vinylamino]benzoate with hydrazine. Spectral data and independent synthesis show that the product is actually 3-amino-4-quinazolone.

Keyphrases □ Methyl 2-[2′,2′-bis(carbethoxy)vinylamino]benzoate—reaction with hydrazine, correction of product structure to 3-amino-4-quinazolone □ 3-Amino-4-quinazolone—product of reaction of methyl 2-[2′,2′-bis(carbethoxy)vinylamino]benzoate with hydrazine, previously assigned 1,3,4-benzotriazepine-5-one structure

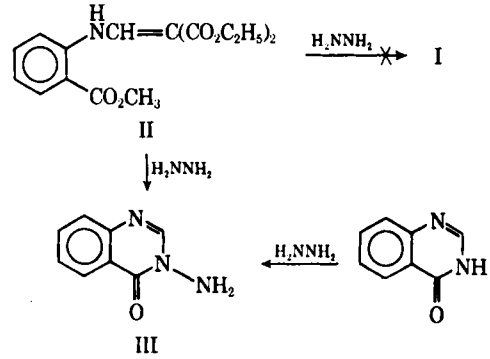
The reaction of methyl 2-[2′,2′-bis(carbethoxy)vinylamino]benzoate with hydrazine was reported by Podesva *et al.* (1) in 1969. These workers obtained a compound, m.p. 214–215°, to which they assigned the 1,3,4-benzotriazepine-5-one structure (I). This reaction



I

appeared to offer a convenient route to additional analogs of I for study as potential psychotherapeutic agents[1].

This transformation has been reproduced, giving a product with a melting point of 214–215°, but the NMR showed the presence of a sharp singlet at 5.87 δ integrating for two protons, a sharp singlet (1H) at 8.35 δ, and a complex multiplet (4H) at 7.31–8.29 δ. The absence in the spectrum of a broad signal due to an amide proton is inconsistent with Structure I. Another possible structure for the product from the reaction of methyl 2-[2′,2′-bis(carbethoxy)vinylamino]benzoate (II) with hydrazine



Scheme I

is the isomeric aminoquinazolone (III, Scheme I). The NMR data are completely consistent with this structure.

An authentic sample of III was prepared from 4-quinazolone (2) and hydrazine according to the method of Leonard and Ruyle (3)[2]. Comparison of the IR and NMR spectra of this compound with the product obtained from II showed them to be identical. In addition, a mixed melting point was undepressed.

By analogy, the compound described as 7-chloro-3,4,5-benzotriazepine-5-one by Podesva *et al.* (1) must also have the corresponding quinazolone structure.

EXPERIMENTAL[3]

Methyl 2-[2′,2′-Bis(carbethoxy)vinylamino]benzoate (II)—This compound was prepared according to the procedure of Podesva *et al.* (1) from 7.55 g. (0.05 mole) of methyl anthranilate and 10.8 g. (0.05 mole) of ethyl ethoxymethylenemalonate. The first crop amounted to 9.62 g. (60%), m.p. 51–55°. Recrystallization from hexane gave clusters of fine white needles, m.p. 56.5–57° [lit. (1) 78% yield, m.p. 71–72°]. Further recrystallizations from hexane did not change the melting point. IR (KBr): 5.9 (broad ester C=O) and 3.11 (NH) μ; NMR ($CDCl_3$): δ 12.62 (broadened d, 1, J = 13.5 Hz., NH), 8.56 (d, 1, J = 13.5 Hz., N—CH), 6.89–8.17 (m, 4, ArH), 4.40 (q, 2, OCH_2), 4.28 (q, 2, OCH_2), 3.98 (s, 3, OCH_3), 1.38 (t, 3, C—CH_3), and 1.33 (t, 3, C—CH_3).

Anal.—Calc. for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 60.09; H, 6.04; N, 4.47.

3-Amino-4-quinazolone (III)—*Method A*—Treatment of 2.50 g. (7.79 mmoles) of II with 1.25 g. (25.0 mmoles) of 100% hydrazine hydrate in 12 ml. of ethanol, according to the procedure of Podesva *et al.* (1), gave a solid which was filtered and washed thoroughly with water. After drying in an evacuated desiccator containing phosphorus pentoxide overnight, 1.03 g. (82%) of colorless glistening needles, m.p. 213–214°, was obtained. Recrystallization from 95% ethanol afforded needles, m.p. 214–215°; IR (KBr): 5.98 (C=O), 6.12 (C=N), and 3.04, 3.17 (NH_2) μ; NMR (dimethyl sulfoxide-d_6): δ 8.35 (s, 1, N=CH—N), 7.31–8.29 (m, 4, ArH), and 5.87 (s, 2, NH_2).

Method B—Colorless needles, m.p. 213.5–215°, were prepared from 4-quinazolone (2) and hydrazine hydrate according to the procedure of Leonard and Ruyle (3). Recrystallization from 95% ethanol gave colorless needles, m.p. 213–214° [lit. (3) m.p. 209–210°]. This compound proved to be identical with the product described in Method A by comparison of their IR and NMR spectra. In addition, a mixed melting point was not depressed.

REFERENCES

(1) C. Podesva, G. Kohan, and K. Vagi, *Can. J. Chem.*, **47** 489(1969).

(2) S. Niementowski, *J. Prakt. Chem.*, **51**, 564(1895).

(3) N. J. Leonard and W. V. Ruyle, *J. Org. Chem.*, **13**, 907(1948).

[1] The only other compound related to I that has been reported in the literature is the 7-chloro analog. It was prepared similarly by the same authors.

[2] The compound obtained by Leonard and Ruyle was characterized as its benzal derivative, thereby ruling out Structure I for this product.

[3] Melting points were determined with a Fisher-Johns apparatus and are corrected. IR spectra were obtained on a Beckman IR-8 spectrophotometer. NMR spectra were determined on a Varian A-60A spectrometer, using tetramethylsilane as the internal reference.

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GLC Determination of Methaqualone in Plasma

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Abstract □ A simple GLC method was developed for the determination of methaqualone in plasma. The method is rapid and quantitative over the 0.1–1.0-mcg./ml. range.

Keyphrases □ Methaqualone—GLC determination in plasma □ GLC—determination of methaqualone in plasma

Methaqualone, 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone, is a well-known compound which has been available for use as a hypnotic since 1960. Determination of this drug in biological fluids has been investigated using spectrophotometric (1) and GC (2, 3) procedures. The former technique is not suitable for precise measurement because of high blank values, while the latter procedure, which eliminates the blank problem, is tedious and time consuming. In addition, it requires 5.0 ml. of plasma. This report describes a GC method for the determination for methaqualone that is simple, rapid, and reliable.

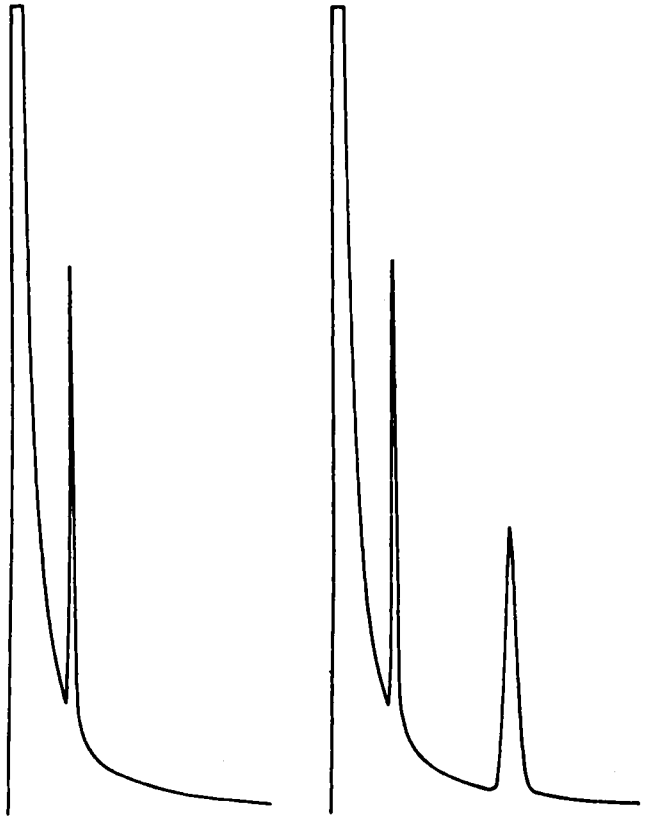

Figure 1—*Gas chromatograms of plasma treated as described. Left: chromatogram from normal plasma. Right: chromatogram from normal plasma with 0.5 mcg./ml. of methaqualone added.*

Table I—Recovery of Methaqualone from Plasma

Methaqualone Added, mcg./ml.	Methaqualone Recovered, mcg./ml.	Percent Recovery[a]
0.20	0.14	70
0.50	0.37	74
1.0	0.77	77
2.0	1.4	70
5.0	3.5	70
10.0	6.9	69
	Average	71.7 ± 1.3[b]

[a] Recoveries are based on a comparison to GC response to pure solutions of methaqualone. [b] Standard error.

Table II—Methaqualone Plasma Concentrations (Micrograms per Milliliter) in Human Subjects[a]

Methaqualone Dose, mg.	Hours						
	0	0.25	0.5	1	2	4	8
400	None detected	0.6	1.7	2.3	1.4	1.1	0.5
800	None detected	1.1	2.3	3.5	4.3	3.5	2.0

[a] Each value given is an average of three subjects.

EXPERIMENTAL

GC—A dual-column gas chromatograph[1] equipped with a hydrogen flame-ionization detector and a 1-mv. recorder[2] was employed. The chromatographic columns used were 0.6-m. (2-ft.) × 0.6-cm. (0.25-in.) glass tubes packed with 3% XE-60 on 100–120-mesh Gas Chrom Q[3]. The instrument settings were: column temperature, 180°; injection port temperature, 240°; and detector block temperature, 230°. Gas flow rates were: hydrogen, 25 ml./min.; and helium (carrier gas), 50 ml./min. Sensitivity settings were: range, 10; and attenuation factor, 2×. The retention times under these conditions were 1.6 min. for butyl stearate and 4.5 min. for methaqualone (Fig. 1).

Reagents—The reagents were redistilled chloroform[4] and butyl stearate[4].

Procedure—Plasma, 1.0 ml., was made alkaline with 0.05 ml. of 1 *N* NaOH, and 0.2 ml. of chloroform containing 0.5 mcg./ml. of

[1] F & M model 402.
[2] Minneapolis-Honeywell.
[3] Applied Science.
[4] Regis Chemical.