Semicarbazones of α,β-Unsaturated 20-Ketosteroids

BY HANS REICH AND RAYMOND W. COLLINS[1]

Some time ago Klyne and co-workers[2] isolated Δ^{16}-allopregnen-3(β)-ol-20-one sulfate from pregnant mare's urine and reported that the free keto-alcohol failed to give a semicarbazone. However, three semicarbazones of 16,17-unsaturated 20-ketosteroids are described in the literature: Δ^{16}-pregnene-3,20-dione disemicarbazone,[3] Δ^{16}-pregnen-3-(β)-ol-20-one semicarbazone[4] and Δ^{16}-pregnen-3(β)-ol-20-one acetate semicarbazone.[4] These semicarbazones were prepared "by treatment with semicarbazide acetate under the usual conditions." In the present experiments we have studied the conditions under which semicarbazones of Δ^{16}-20 ketosteroids are formed, and have prepared three additional compounds of this type.

We found that the reaction of $\Delta^{5,16}$-pregnadien-3-(β)-ol-20-one, its acetate and Δ^{16}-allopregnen-3(α)-ol-20-one acetate with semicarbazide acetate in ethanol was incomplete after refluxing for 1.5 hours. The crude reaction products showed maximum absorption at 240 mμ (starting material) and only an inflection between 260 and 270 mμ. When the ketosteroids were refluxed with the same semicarbazide acetate solution for 24 hours, the crude reaction products as well as the crystals isolated from them showed only a single maximum at 267 mμ. The same was the case when the reaction was carried out at room temperature in the presence of pyridine.[5] A similar absorption maximum was found by Wettstein[6] for the semicarbazone of $\Delta^{5,16}$-16-methylpregnadien-3(β)-ol-20-one acetate. Since displacement to longer wave lengths is usually observed in passing from the carbonyl compound to its semicarbazone,[7] the absorption maximum at 267 mμ indicates that normal semicarbazones of 16,17-unsaturated 20-ketosteroids were formed. This maximum excludes the formation of a pyrazoline derivative as well as the addition of one mole of semicarbazide to the quite reactive Δ^{16}-double bond.[6,8] In the latter case there would result a saturated ketone which should show only a band of low intensity with a maximum in the region of 280–300 mμ,[9] while pyrazoline derivatives show nearly the same absorption maxima as the parent ketones.[10]

In contrast to the slow formation of semicarbazones of 16,17-unsaturated 20-ketosteroids the corresponding saturated ketones and those with a hydroxyl group in 17α-position react readily with semicarbazide.[11]

Experimental[12]

Semicarbazide Acetate Solution.—One hundred mg. of semicarbazide hydrochloride and 150 mg. of sodium acetate trihydrate were ground until the mixture liquefied. Then it was taken up in absolute ethanol, filtered and the filtrate diluted to 10 cc.

Semicarbazones.—20–30 mg. of ketone was refluxed for 24 hours with 2–3 cc. of semicarbazide acetate solution. After cooling the solution was concentrated *in vacuo*, diluted with water and extracted twice with chloroform. The chloroform solutions were washed once with water, dried and evaporated. The residue was recrystallized twice from abs. ethanol.

$\Delta^{5,16}$-Pregnadien-3(β)-ol-20-one Semicarbazone.—This semicarbazone decomposed gradually above 230° and did not melt up to 300°; maximum at 267 mμ (log *E* 4.342). *Anal.* Calcd. for $C_{22}H_{33}O_2N_3$: N, 11.31. Found: N, 11.76.

$\Delta^{5,16}$-Pregnadien-3(β)-ol-20-one Acetate Semicarbazone.[13]—M.p. 209.5–212°; maximum at 267 mμ (log *E* 4.380). *Anal.* Calcd. for $C_{24}H_{35}O_3N_3$: C, 69.70; H, 8.53; N, 10.16. Found: C, 69.24; H, 8.09; N, 10.13.

Δ^{16}-Allopregnen-3(α)-ol-20-one Acetate Semicarbazone.—M.p. 216–219°; maximum at 267 mμ (log *E* 4.387). *Anal.* Calcd. for $C_{24}H_{37}O_3N_3$: N, 10.11. Found: N, 9.80.

The same semicarbazone was also obtained as follows: a solution of 500 mg. of semicarbazide hydrochloride in 1.5 cc. of water was mixed with a solution of 500 mg. of potassium acetate in 5 cc. of abs. ethanol. The potassium chloride was filtered off, and 0.5 cc. of the filtrate was added to a solution of 11 mg. of the ketone in 0.5 cc. of abs. ethanol-pyridine 1:1. After addition of one drop of water the mixture was allowed to stand at room temperature for 4 days. It was then diluted with water and extracted three times with ether. The ether solutions were washed neutral, dried and evaporated. Two recrystallizations from abs. ethanol gave crystals of m.p. 214–217°; maximum at 267 mμ.

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[1] This investigation was supported in part by research grants from the National Cancer Institute of the National Institutes of Health, Public Health Service, and from Ciba Pharmaceutical Products, Inc., Summit, N. J.

[2] W. Klyne, B. Schachter and G. F. Marrian, *Biochem. J.*, **43**, 231 (1948).

[3] R. E. Marker and E. Rohrmann, THIS JOURNAL, **62**, 518 (1940).

[4] R. E. Marker and E. Rohrmann, *ibid.*, **62**, 521 (1940).

[5] J. D. Dutcher and O. Wintersteiner, *ibid.*, **61**, 1992 (1939).

[6] A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944).

[7] L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 565 (1943).

[8] D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **72**, 2306 (1950).

[9] L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publishing Corp., New York, N. Y. 1949, p. 190.

[10] K. Dimroth and O. Lüderitz, *Ber.*, **81**, 242 (1948).

[11] For instance pregnenolone acetate, *ibid.*, **67**, 1611 (1934); progesterone, *J. Biol. Chem.*, **107**, 321 (1934); Cpd. E, *Helv. Chim. Acta*, **19**, 29 (1936).

[12] M.p's. were taken on a Kofler micro hot stage and are corrected. The quantitative ultraviolet spectra were carried out by Mr. L. Dorfman, Ciba Pharmaceutical Products, Summit, N. J. Two samples of ketones were kindly supplied by Dr. M. Tishler, Merck & Co., Inc., Rahway, N. J., and Dr. J. J. Pfiffner, Parke, Davis & Co., Detroit, Mich.

[13] After completion of our experiments an article by R. Fischer, G. Lardelli and O. Jeger appeared (*Helv. Chim. Acta*, **33**, 1335 (1950)) in which the preparation of this semicarbazone is described. After reflux for 8 hours only half of the ketone had been converted to the semicarbazone.

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No Insecticidal Activity of 1,1,4,4-Tetra-[*p*-chlorophenyl]-2,2,3,3-tetrachlorobutane

BY R. RIEMSCHNEIDER

Bernimolin[1] has reported that 1,1,4,4-tetra-[*p*-chlorophenyl]-2,2,3,3-tetrachlorobutane (I), mol. wt. 638, shows the same degree of toxicity as *p,p'*-DDT (II) against *Drosophila melanogaster M.* High toxicity of I is unexpected because of its molecular weight, high melting point (270°) and slight lipoid solubility.

We have determined by means of film tests (Petri dishes) the toxicity of I against *Drosophila*. No symptoms of poisoning were exhibited after 300 minutes when 2000 γ of I were used; under the

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[1] J. Bernimolin, THIS JOURNAL, **71**, 2274 (1949).

same conditions 10 γ of II caused 100% mortality. It is possible that Bernimolin's I contained II or even that it was not identical with I prepared from II by the method of Brand and Bausch.[2] Bernimolin's assumption that the presence of I (perhaps formed by irradiation of II) may be partly responsible for the extraordinary residual effect of II cannot be correct. Likewise Bernimolin's conclusion, based on the supposed insecticidal activity of I, that the molecular weight of residually active contact insecticides of the halohydrocarbon type is not limited, is without foundation.

The alteration of physical properties, *e.g.*, the decrease in lipoid solubility, with increase in molecular weight corresponds in our experience[3] with a quite general lowering of contact insecticidal activity of halogenated hydrocarbons when their molecular weight exceeds 430–450. Halogenated hydrocarbons whose molecular weight exceeds this limiting value are not necessarily completely inactive as contact insecticides. Thus in 1947 we reported[4] insecticidal activity for the substance M 490 (so called because of its approximate molecular weight). This activity, however, was much less than that of M 410[5] (Chlordane).

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(2) Brand and Bausch, *J. prakt. Chem.*, **127**, 232 (1930).

(3) R. Riemschneider, "Zur Kenntnis der Kontakt-Insektizide I," Beiheft 2, Ergänzungsband 1 zur "Pharmazie" 1947. A paper of Lord (*Ann. Appl. Biol.*, **35**, 505 (1948)) confirms the supposition made in this book that the molecular weight of highly active contact insecticides of the halohydrocarbon type with residual effect is limited.

(4) Riemschneider, *Mitt. Physiol. Chem. Inst.*, *R12*, Dec., 1947, and *R11*, Oct., 1947.

(5) Riemschneider, *Pharmazie*, **3**, 115 (1948); *Chem. Z.*, II, 344 (1948); *Chim. et Ind.*, **64**, 695 (1950).

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The System $Ba(IO_3)_2$–$BaCl_2$–H_2O at 25°

BY JOHN E. RICCI

In connection with studies on the aqueous phase relations of the halates, the 25° isotherm of the system $Ba(IO_3)_2$–$BaCl_2$–H_2O was investigated, revealing the formation of an incongruently soluble hydrated double salt with the probable formula $Ba(IO_3)_2 \cdot BaCl_2 \cdot 2H_2O$. The results, in terms of weight percentage, are listed in Table I and plotted in Fig. 1.

The general procedure was that described in similar reports. Complexes were made up from water and the solids $Ba(IO_3)_2 \cdot H_2O$ and $BaCl_2 \cdot 2H_2O$, which were C.P. samples checked for purity by direct analysis. After 1 or 2 weeks of stirring the filtered saturated solution was analyzed for iodate with standard thiosulfate and for total solid by evaporation. Reanalysis after a similar additional period of stirring was used to prove equilibrium. The double salt did not form readily. A practically complete but metastable diagram was obtained with the separate hydrated salts as sole solid phases, before the double salt, suspected because of unsatisfactory aspects of the first diagram, could be made to form; thereafter it was used to seed the various complexes. After such seeding, for example, the remaining liquid of complex no. 6 dropped in composition to that shown as line 8 of the table; the "total complex" composition for line 8 was estimated from that of no. 6 corrected for the amount of liquid withdrawn for analysis before seeding. Line 9 bears the same relation to line 7.

TABLE I

SYSTEM $Ba(IO_3)_2$–$BaCl_2$–H_2O AT 25°

	Saturated solution Wt. %			Total complex wt. %		Solid
	$Ba(IO_3)_2$	$BaCl_2$	Density	$Ba(IO_3)_2$	$BaCl_2$	phase[b]
1	0.0400	0.00	0.997	...	0.00	A
2	.0189	19.63	1.194	8.00	18.00	A
3	.0187	20.50	1.206	25.99	14.99	A
4	.0198	21.56	1.218	7.00	20.00	A
5	.0231	25.29	1.268	23.82	19.07	A^m
6	.0240	25.59	1.273	23.52	21.47	A^m [a]
7	.0267	27.09	1.286	23.58	21.54	$(A + C)^m$
8		22.06	1.222	35.3	19.6	A + B
9		22.05	1.223	29.5	20.2	A + B
10	.0201	(22.38)?		6.01	21.36	A + B
11	.0201	22.06	1.225	6.03	22.16	A + B
	.0201	22.06	1.223	= average		A + B
12	.0189	22.72	1.232	6.03	23.24	B
13	.0186	23.76	1.245	5.99	24.17	B
14	(.020)	24.25	1.255	10.96	24.96	B
15	.0179	24.73	1.258	6.00	25.04	B
16	.0171	25.45	1.266	6.00	25.72	B
17	(.019)	25.51	1.269	10.02	25.96	B
18	.0165	26.01	1.274	6.04	26.22	B
19	.0152	26.82	1.285	5.89	26.95	B
20	.0153	27.09	1.289	4.99	27.95	B + C
21	.0153	27.11	1.289	2.00	39.95	B + C
22	.00	27.11	1.289	0.00	...	C

[a] Probably in course of change, not completely at equilibrium. [b] A = $Ba(IO_3)_2 \cdot H_2O$; B = $Ba(IO_3)_2 \cdot BaCl_2 \cdot 2H_2O$; C = $BaCl_2 \cdot 2H_2O$; *m* = metastable.

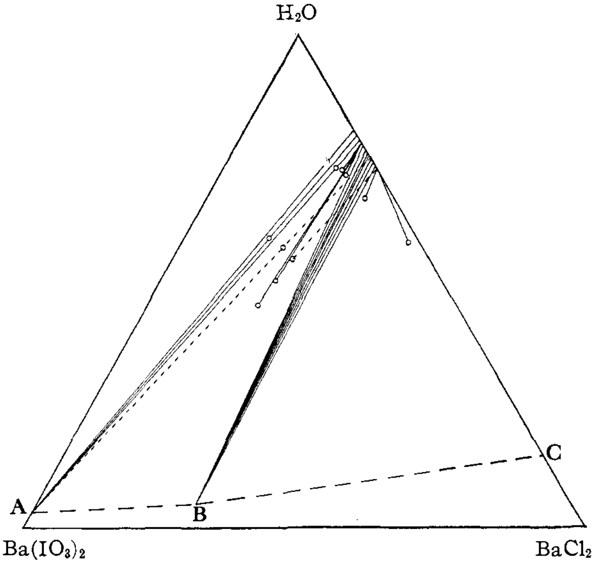

Fig. 1.—25° isotherm of system $(BaIO_3)_2$–$BaCl_2$–H_2O; A = $Ba(IO_3)_2 \cdot H_2O$, B = $Ba(IO_3)_2 \cdot BaCl_2 \cdot 2H_2O$, C = $BaCl_2 \cdot 2H_2O$.

The formula of the double salt was determined by the intersection of the tie-lines fixed by the compositions of saturated solution and total complex.[1] For greater dependability of the extra-

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(1) A. E. Hill and J. E. Ricci, THIS JOURNAL, **53**, 4305 (1931).