amide in 300 ml. of anhydrous benzene was heated under reflux for 3 hr. 3-Chloro-*N,N*-dimethylpropylamine, 16.5 g. (0.13 mole), in 50 ml. of anhydrous benzene was added dropwise over a 30-min. period and the mixture was heated under reflux with stirring for an additional 5 hr. The excess sodium amide was decomposed with 25 ml. of ethanol followed by 50 ml. of water. The aqueous phase was separated and extracted with ether. The benzene and ether phases were combined, washed with water and then extracted with two 100-ml. portions of *N* hydrochloric acid. The acidic extracts were made alkaline with excess sodium carbonate, and extracted several times with ether. The ether extracts were dried and evaporated. Distillation of the residue yielded 21.0 g. (73% yield) of product, b.p. 152–155°/0.5 mm.

Anal. Calcd. for $C_{17}H_{21}ClN_2$ (288.82): C, 70.7; H, 7.33; Cl, 12.3; N, 9.70. Found: C, 69.9; H, 7.58; Cl, 12.3; N, 9.84.

The hydrochloride melted at 138–139°.

Anal. Calcd. for $C_{17}H_{21}ClN_2 \cdot HCl$ (325.28): C, 62.8; H, 6.81; Cl, 21.8; N, 8.61. Found: C, 62.4; H, 6.93; Cl, 22.1; N, 8.36.

α-(3-Dimethylaminopropyl)-o-hydroxybenzhydrol (XIV). The Grignard reagent was prepared according to Procedure A from 5.75 g. (0.236 g.-atom) of magnesium and 28.7 g. (0.236 mole) of 3-chloro-*N,N*-dimethylpropylamine in 250 ml of ether. *o*-Methoxybenzophenone,[31] 25 g. (0.118 mole), in 200 ml. of ether was added in small portions. The reaction mixture was heated under reflux for 16 hr., cooled and decomposed with 250 ml. of a cold 10% aqueous ammonium chloride solution. The organic phase was separated and extracted with 250 ml. of 0.5*N* hydrochloric acid. The acidic aqueous phase was made alkaline with potassium carbonate and extracted with ether. The dried ether extract was evaporated to a solid residue. Recrystallization from ethanol yielded 20 g. (56.5%) of product, m.p. 116–117°.

Anal. Calcd. for $C_{18}H_{23}NO_2$ (385.37): C, 75.8; H, 8.12; N, 4.91. Found: C, 75.0; H, 8.06; N, 4.90.

o-(4-Dimethylamino-1-phenyl-1-butenyl)phenol hydrochloride (XV). A mixture of 5 g. (0.018 mole) of α-(3-dimethylaminopropyl)-*o*-hydroxybenzhydrol (XIV), 10 ml. of concd. hydrochloric acid, and 30 ml. of glacial acetic acid was heated under reflux for 3 hr., cooled, diluted with 75 ml. of water, and made alkaline with an excess of potassium carbonate. The free base was extracted with ether and converted to the hydrochloride in the usual way. The yield of the hydrochloride was 4.0 g. (70%), m.p. 184–185°.

Anal. Calcd. for $C_{18}H_{21}NO \cdot HCl$ (303.83): C, 71.2; H, 7.30; Cl, 11.7; N, 4.61. Found: C, 71.0; H, 7.22; Cl, 12.2; N, 4.57.

9-(3-Dimethylaminopropyl)fluoren-9-ol (XVII). The Grignard reagent was prepared from 4.9 g. (0.2 g.-atom) of magnesium and 24.3 g. (0.2 mole) of 3-chloro-*N,N*-dimethylpropylamine in 150 ml. of ether as described in Procedure A. Fluoren-9-one, 18.1 g. (0.1 mole), in 150 ml. of benzene was added and the reaction mixture (a yellow suspension) was heated under reflux until all the magnesium was consumed (30 hr.). The reaction was worked up according to Procedure B, and the fluoren-9-ol derivative was isolated as the free base. Recrystallization from alcohol afforded 8.0 g. (30% yield) of product, m.p. 101–103°.

Anal. Calcd. for $C_{18}H_{21}NO$ (267.36): C, 80.9; H, 7.92; N, 5.24. Found: C, 80.6; H, 7.95; N, 5.37.

N,N-Dimethylfluoren-Δ$^{9,\gamma}$-propylamine hydrochloride (XVI). Six grams (0.02 mole) of 9-(3-dimethylaminopropyl)-fluoren-9-ol in 100 ml. of ether was dehydrated by passing hydrogen chloride through the solution for 15 min. The reaction mixture was evaporated and the residue was dissolved in water. The aqueous solution was made alkaline with 10% sodium hydroxide and extracted with ether. The product was isolated as the hydrochloride from the ethereal solution by the addition of alcoholic hydrogen chloride. Recrystallization from alcohol-ether afforded 4.5 g. (71% yield) of product, m.p. 205–207°.

Anal. Calcd. for $C_{18}H_{19}N \cdot HCl$ (285.81): C, 75.6; H, 7.05; Cl, 12.4; N, 4.90. Found: C, 75.4; H, 7.35; Cl, 12.5; N, 5.18.

Acknowledgment. We are indebted to N. Q. Quinones, L. H. Yogodzinski, and Miss B. A. Carpentier for their technical assistance; J. H. Clark and his group for the preparation of some of the intermediates; L. Brancone and associates for the microanalyses; and W. Fulmor and associates for the spectral data.

PEARL RIVER, N. Y.

(31) T. Tasaki, *Acta Phytochim.*, **2**, 49 (1925); *Chem. Abstr.*, **20**, 1030 (1926).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Synthesis of Potential Anticancer Agents. IX. Lawsone Derivatives Containing an Alkylating Function[1,2]

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Received July 8, 1960

The Mannich reaction involving lawsone (2-hydroxy-1,4-naphthoquinone) and certain amines with formaldehyde and acetaldehyde has been carried out using modifications of a published procedure. In addition, the condensation product of lawsone with 4-bis(2-chloroethyl)aminobenzaldehyde is described.

It has been reported that lawsone (2-hydroxy-1,4-naphthoquinone) undergoes the Mannich reaction with a variety of primary and secondary amines including ethanolamine and morpholine, but not with diethylamine.[3] With the latter the reaction affords instead what appeared to be the diethylamine salt of 3,3′-methylenebis(2-hydroxy-1,4-naphthoquinone) (I).

(1) Previous paper in this series, P. Scheiner and W. R. Vaughan, *J. Org. Chem.*, 26, 1923 (1961).

(2) This work supported by Research Grant CY-2961 from the National Cancer Institute to the University of Michigan.

(3) M. T. Leffler and R. J. Hathaway, *J. Am. Chem. Soc.*, **70**, 322 (1948).

Although the latter information would appear to be discouraging if one wished to use aziridine (ethylenimine), bis (2-chloroethyl)amine, or diethanolamine, it was believed that further exploration would reveal experimental conditions for satisfactory reaction. To this end the reaction of lawsone, formaldehyde, and morpholine was repeated with substantially the reported results[3] to give 4 - (4′ - morpholino)methyl - 2 - hydroxy - 1,4-naphthoquinone (II), but when exactly the same procedure was applied to diethanolamine, an orange precipitate was obtained which appeared to be the diethanolamine salt of I, since on treatment with dilute hydrochloric acid I was obtained. Thus it would appear that the course of the reaction was similar to that encountered by Leffler and Hathaway with diethylamine.[3]

Several modifications in the procedure were investigated, and finally it was found that addition of solid lawsome to a solution of diethanolamine[4] and formalin in absolute ethanol at 30–35° afforded an acid-soluble product which could be recovered from 5% hydrochloric acid by addition of sodium acetate. Microanalysis indicated that the product was a monohydrate of the expected 3- bis(2′ - hydroxyethyl)aminomethyl - 2 - hydroxy - 1,4 - naphthoquinone (III). However, any and all attempts to effect recrystallization resulted in decomposition with the apparent production of the diethanolamine salt of I originally encountered, for I was produced from it on treatment with 5% hydrochloric acid. Likewise, all attempts to convert II or III to 3-bis(2′-chloroethyl)aminomethyl-2- hydroxy - 1,4 - naphthoquinone (IV), the corresponding nitrogen mustard, resulted in production of a salt of I.

When ethylenimine was used in the Mannich reaction with lawsone and formaldehyde, it was found necessary to add the lawsone to the other reagents at 4–6°, whereupon a good yield of 3-aziridinomethyl - 2 - hydroxy - 1,4 - naphthoquinone (V) was obtained as a hydrate. The product was found to be slightly soluble in ice-cold 2% hydrochloric acid, from which it is recoverable if sodium acetate is added immediately. On standing the acidic solution deposits I, which is also obtained, presumably as the ethyleneimine salt, upon all attempts to effect recrystallization.

The possibility that azetidine derivatives might behave analogously to ethylenimine derivatives as "alkylating agents" has been suggested elsewhere.[5] With this in mind the reaction of lawsone, formaldehyde, and azetidine was carried out in a fashion similar to the ethylenimine reaction with satisfactory results. A 50% yield of 3-*N*-azetidinomethyl - 2 - hydroxy - 1,4 - naphthoquinone (VI) was obtained, and this substance proved to be comparatively stable. Indeed it was recrystallizable from methanol.

The reaction of lawsone and formaldehyde with nitrogen mustard (bis(2-chloroethyl)amine), proved very difficult, but it was finally found that the most satisfactory procedure for carrying out the Mannich reaction with lawsone and secondary amines of the type desired involved addition of an ethanol solution of lawsone to the amine and formaldehyde in absolute ethanol at low temperature. In this manner the condensation product constitutes the only solid present at any time in the reaction mixture; and by careful manipulation II, III, and IV can be obtained analytically pure.

As a check on the superior character of this technique for sensitive compounds, diethylamine was similarly condensed, and a satisfactory yield of the previously unavailable[3] 3-diethylaminomethyl-2-hydroxy-1,4-naphthoquinone (VII) was obtained.

The behavior of compounds III—V with dilute hydrochloric acid and with glacial acetic acid deserves some comment. Compound III is apparently soluble and stable in dilute hydrochloric acid; V with ice-cold 2% hydrochloric acid appears to form a semihydrochloride (VIII) which is rather insoluble and which decomposes on standing in contact with the acid; and both IV and V decompose at once with more concentrated hydrochloric acid even at 0°. In all hydrochloric acid decompositions I is precipitated, and the change is readily observed, since the red Mannich products rapidly become bright yellow as I is produced from them.

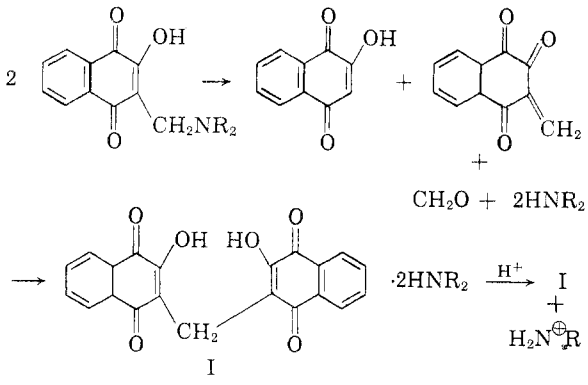
With glacial acetic acid IV immediately decomposes to give I while the others do so more slowly, the relative rates being in the order: IV > V > VIII > III < VII. Furthermore, each of these substances affords the diacetate of I[6] when treated with acetic anhydride containing a drop of concentrated sulfuric acid.

In the absence of acids the same type of decomposition is encountered, though more slowly, and appears to be heat-induced, although the acidic character of the lawsone hydroxyl may provide a weak autocatalysis. For example, when only one equivalent of sodium acetate is used to "neutralize" a hydrochloric acid solution of III, the decomposition is rapid, whereas an excess of sodium acetate regenerates III smoothly. It would appear that this decomposition involves a reversal of the Mannich reaction to produce 3-methylene-1,2,4-trioxotetralin and lawsone which then react by addition to give I. Where an acid is present I precipitates directly; otherwise, the corresponding amine salt is formed.

(4) The procedure developed herein differs from that of C. L. Dalgliesh, *J. Am. Chem. Soc.*, 71, 1697 (1949), in that the amine is always present in excess and thus the medium is always alkaline. Consequently, the *free* amine is available, and this is what is required for the production of the C—N bond.

(5) W. R. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, 26, 138 (1961).

(6) L. F. Fieser, M. T. Leffler, *et al.*, *J. Am. Chem. Soc.*, 70, 3212 (1948).



Inasmuch as lawsone condenses readily with aldehydes other than formaldehyde to give analogs of I[4,6], *e.g.*, with 4-dimethylaminobenzaldehyde, the procedure for condensation of the latter was applied to 4-bis(2-chloroethyl)aminobenzaldehyde,[7] with some modification, and there was obtained in fair yield di(2 - hydroxy - 1,4 - naphthoquinon - 3-yl) - 4 - bis(2 - chloroethyl)aminophenylmethane (IX). Considerable difficulty was encountered in purifying this substance, substantial decomposition to unidentified materials occurring in most cases, but recrystallization was finally effected by dissolving the crude product in dimethylformamide at room temperature and then adding the solution dropwise to a large excess of ethanol.

Acetaldehyde has been rarely used in Mannich reactions, but a search of the literature revealed that open chain compounds from a Mannich-type reaction when acetaldehyde was employed were available with Lawsone.[4]

When aldehydes other than formaldehyde enter into a Mannich-type reaction, the amines are generally limited to ammonia or primary amines and their salts. It was therefore interesting to note that we encountered no difficulty using secondary amines, as well as primary amines. The compounds were generally obtained from the reaction mixture in pure form. If the reaction mixture required working up, room temperature to moderate temperatures were employed without subsequent recrystallization. As for the formaldehyde reactions, the yields were low in certain instances, as the reaction was often accompanied by dark, intractable tars.

Eight compounds derived from acetaldehyde have been prepared, two of which were derived from primary amines and the others from secondary amines. It is interesting to note that the nitrogen mustard compound was chromophorically different from the others, in that it was obtained as a bright yellow compound, while the others were consistently orange, red, or reddish brown.

(7) R. C. Elderfield, I. S. Covey, J. B. Geiduschek, W. L. Meyer, A. B. Ross, and J. H. Ross, *J. Org. Chem.*, **23**, 1749 (1958).

EXPERIMENTAL[8,9]

3,3'-Methylene-bis(2-hydroxy-1,4-naphthoquinone) (I). This substance was prepared essentially as described by Fieser.[5]

3-Bis(2'-hydroxyethyl)aminomethyl-2-hydroxy-1,4-naphthoquinone (III). (A) *Using solid lawsone.* To a solution of 2.8 ml. of 37% formalin and 3.8 g. (0.036 mole) of redistilled diethanolamine in 50 ml. of absolute ethanol was added with mechanical stirring 5.8 g. (0.033 mole) of lawsone in portions over 45 min., the temperature being maintained at 30–35° by a water bath. Stirring was continued for 4 hr. at the same temperature during which time golden red needles slowly precipitated. The mixture was filtered, washed with 25 ml. of absolute ethanol and then with water, after which the precipitate was dissolved in *ca.* 100 ml. of 2% hydrochloric acid, filtered from a trace of residue, and then treated with a solution of 10 g. of anhydrous sodium acetate in 25 ml. of water. After overnight standing in the refrigerator the product was filtered off and dried in air at 50°: 8.2 g. (85%), m.p. 111.5° (softens), gradually darkening above 150° and liquefying at 192–198°.

Anal. Calcd. for $C_{15}H_{17}NO_5 \cdot H_2O$: C, 58.24; H, 6.19; N, 4.53. Found[10]: C, 58.47; H, 6.10; N, 4.26, 4.31.

(b) *Using lawsone solution.* To 2.8 ml. of 37% formalin and 3.8 g. (0.036 mole) of diethanolamine there was added with efficient stirring over a 4-hr. period a filtered solution of 4.9 g. (0.028 mole) of lawsone in 450 ml. of absolute ethanol. The temperature was maintained at 23–25° by a water bath. At the end of the addition there was added 50 ml. of absolute ethanol, and stirring was continued for 30 min. The orange-red precipitate, which appeared in the initial stages of the reaction, was filtered off and washed with two 50-ml. portions of absolute ethanol: 5.5 g. (68%), slow decomposition from 158–172°. The analytical sample was dried *in vacuo* at room temperature over phosphorus pentoxide.

Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.86; H, 5.87; N, 4.81. Found: C, 61.89; H, 5.85; N, 4.78.

Purification of this product by solution in 2% hydrochloric acid with reprecipitation by sodium acetate as in the previous experiment produced no change after the product was dried *in vacuo* over phosphorus pentoxide. When the reprecipitation was effected by using but one equivalent of sodium acetate, only I was recoverable, as shown by melting point and mixed melting point.

3-Bis(2'-chloroethyl)aminomethyl-2-hydroxy-1,4-naphthoquinone (IV). To a suspension of 1.5 g. (0.0084 mole) of bis(2-chloroethyl)amine hydrochloride in 20 ml. of ether was added 0.75 g. (0.0090 mole) of sodium bicarbonate in 15 ml. of water. The mixture was shaken and separated, and the aqueous layer was extracted with two 20-ml. portions of ether. The combined ethereal solutions were placed in the reaction vessel and the ether removed at reduced pressure, and to the free nitrogen mustard was added 25 ml. of absolute ethanol containing 0.4 ml. of 37% formalin. The mixture was cooled and maintained at 14–16° while a filtered solution of 0.8 g. (0.0046 mole) of lawsone in 80 ml. of absolute ethanol was added over 1 hr., with magnetic stirring. During the addition an orange solid separated, and stirring was continued for 45 min. after completion of the addition—until the mixture reached room temperature (after removal of the cooling bath). The product was filtered with suction and repeatedly washed with ethanol: 0.70 g. (46%), darkens slowly above 125°. The analytical sample was dried as for III (B).

Anal. Calcd. for $C_{15}H_{15}Cl_2NO_3$: C, 54.89; H, 4.60; Cl, 21.61; N, 4.27. Found: C, 55.16; H, 4.78; Cl, 21.73; N, 4.19.

(8) Melting points, taken in open capillaries, are uncorrected.

(9) Microanalyses by Spang Microanalytical Laboratories, Ann Arbor, Mich., unless otherwise indicated.

(10) Carbon and hydrogen analysis by Mrs. Anna Griffen, University of Michigan.

TABLE I

3-AMINOETHYLIDENE-2-HYDROXY-1,4-NAPHTHOQUINONES[a,s]

R_1	R_2	Reaction Temp.	Notes	Yield, %	Dec.[b]	Calcd. for	C	H	N	Cl
C_2H_5[c]	H	5	[d]	36.6	148	$C_{14}H_{15}NO_3$	68.55	6.16	5.71	
						Found	68.53	6.25	5.73	
$HOCH_2CH_2$	H	40	[e]	12.8	124	$C_{14}H_{15}NO_4$	64.35	5.78	5.36	
						Found	64.18	5.68	5.27	
C_2H_5	C_2H_5	25[f]	[g]	4.8	185	$C_{16}H_{19}NO_3$	70.30	7.02	5.12	
						Found	70.36	6.85	4.91	
$HOCH_2CH_2$	$HOCH_2CH_2$	5–10	[h]	21.7	121–122	$C_{16}H_{19}NO_5$	62.93	6.29	4.58	
						Found	63.06	6.47	4.68	
$ClCH_2CH_2$	$ClCH_2CH_2$[i]	5–10	[j]	15.6	156–157[k]	$C_{16}H_{17}Cl_2NO_3$	56.16	5.00	4.09	20.72
						Found	56.41	5.28	3.53	20.56
$—(CH_2)_5—$		20–25[l]	[m]	30.0	169[n]	$C_{17}H_{19}NO_3$	71.55	6.73	4.91	
						Found	71.67	6.97	4.92	
$—(CH_2)_2O(CH_2)—$		20–25	[o]	5.8	154	$C_{16}H_{17}NO_4$	66.89	5.95	4.87	
						Found	66.89	6.09	4.59	
$—(CH_2)_2—$		20–25[p]	[q]	0.2 g.[r]	164	$C_{14}H_{13}NO_3 \cdot {}^1/_2H_2O \cdot {}^1/_4C_2H_5N$	66.45	5.50	6.67	
						Found	66.23	5.55	6.50	

[a] See general procedure immediately preceding. [b] Where no range is reported, product decomposes slowly above recorded temperature. [c] A 70% aqueous solution of ethylamine was used. [d] After the reaction 50 ml. of dry ether was added and the solution filtered after 3 days refrigeration. [e] The reaction was stirred at 40° overnight, then refrigerated. Product washed with ethanol also. [f] Only 80 ml. of absolute ethanol used for lawsone. [g] After reaction, the solution was air-evaporated to 40 ml.; then diluted with 40 ml. of ether and cooled. [h] After reaction, the solvent was removed *in vacuo* at 40–50°. Then 40 ml. of dry ether was added and the solution refrigerated. [i] The mustard hydrochloride (1.5 g.) was suspended in ether and extracted with 0.75 g. of sodium bicarbonate in 15 ml. of water. Aldehyde in 10 ml. absolute ethanol was added to ether solution of free mustard. [j] After the reaction was stirred for 30 min. at room temperature, the product was washed with ethanol alone. [k] Product bright yellow. [l] Amine and aldehyde in 15 ml. absolute ethanol, lawsone in 75 ml. [m] After the reaction, the solvent was evaporated in air stream to 10 ml. [n] Original product recrystallized from ethanol-ether and washed with ether. [o] After the reaction was refrigerated, it was filtered and washed with ethanol alone. [p] Amine and aldehyde in 15 ml. absolute ethanol. [q] After the reaction was stirred for 30 min., it was refrigerated for several hours, filtered, and washed with ethanol alone. [r] Product was not the expected pure 3-aziridinoethylidene-2-hydroxy-1,4-naphthoquinone. [s] These data added to original manuscript: received December 2, 1960.

3-Aziridinomethyl-2-hydroxy-1,4-naphthoquinone (V). Using essentially the procedure described above (for III (A)) with 2.8 ml. of 37% formalin, 1.6 g. (1.9 ml.) of ethylenimine (aziridine), 50 ml. of absolute methanol, and 5.8 g. (0.033 mole) of lawsone (30 min. portionwise addition at 4–6°), there was obtained 7.2 g. (98%) of bright red product which chars slowly above 162°.

Anal. Calcd. for $C_{13}H_{11}NO_3 \cdot H_2O$: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.68; H, 5.40; N, 5.42.

No satisfactory recrystallization could be effected, but an unaltered product is recoverable from cold 2% hydrochloric acid, in which it is not appreciably soluble, by treatment with sodium acetate. Upon shaking a 0.5-g. sample in 75 ml. of ice-cold 2% hydrochloric acid for 5 min. and filtering off the residual solid and washing it with water, there was obtained 0.49 g. of a substance which darkens slowly above 140° (VIII).

Anal. Calcd. for $C_{13}H_{11}NO_3 \cdot H_2O.1/2HCl$: C, 58.81; H, 5.13; Cl, 6.68; N, 5.27. Found: C, 58.70; H, 5.19; Cl, 6.35; N, 5.37.

From the acidic filtrate from VIII, upon addition of sodium acetate there was recovered a small amount of V, identified by infrared spectrum. A small sample of VIII was treated with 5% sodium bicarbonate, and the red precipitate was filtered from the dark red solution (not observed on similar treatment of V), which was then treated with dilute nitric acid and centrifuged from an orange precipitate (I) and treated with silver nitrate to give silver chloride.

3-N-Azetidinomethyl-2-hydroxy-1,4-naphthoquinone (VI). This substance was prepared essentially as for V (A) using 2.8 ml. of 37% formalin, 2.0 g. (0.035 mole) of azetidine[5] (in 50 ml. of absolute ethanol), and 5.8 g. (0.033 mole) of solid lawsone, added over 30 min. at 4–6°. After complete addition, 25 ml. more absolute ethanol was added and stirring was continued for 5 hr. while the temperature was allowed to rise slowly to 25°. Filtration and drying afforded 4.05 g. (50%) of brick-red product: after recrystallization from methanol, dull red needles, indefinite decomposition above 160°.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.14; H, 5.42; N, 5.34 (0.40% ash).

3-Diethylaminomethyl-2-hydroxy-1,4-naphthoquinone (VII). To a stirred solution of 0.5 ml. of 37% formalin and 0.6 g. (0.008 mole) of diethylamine in 15 ml. of absolute ethanol was added a filtered solution of 1.0 g. (0.006 mole) of lawsone in 100 ml. of absolute ethanol (1 hr. 50 min. at 10–15°). No separation of solid was observed, even after cooling to 0°. Consequently the solvent was evaporated at room temperature in an air stream, whereupon a deep red (almost violet) precipitate was obtained. After suction filtration and several washings with small amounts of cold ethanol there was obtained 1.3 g. (83%): m.p., 145.0–147.5° dec.

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.49; H, 6.59; N, 5.40. Found[11]: C, 69.31; H, 6.79; N, 5.52.

This substance dissolved in hot acetic acid with the immediate precipitation of I.

Di(2-hydroxy-1,4-naphthoquinon-3-yl)-4-bis(2-chloroethyl)-aminophenylmethane (IX). A solution of 9.1 g. (0.051 mole) of lawsone in 125 ml. of ethanol and a filtered solution of 6.2 g. (0.025 mole) of 4-bis(2-chloroethyl) aminobenzaldehyde[7] in 100 ml. of ethanol were mixed and heated under reflux for 4 hr. after which time the solution was concentrated under reduced pressure to 100 ml. and filtered hot. The brick-

(11) Microanalysis by Galbraith Laboratories, Knoxville, Tenn.

red residue (6.0 g.) was dissolved in *ca.* 8 ml. of dimethylformamide at room temperature, and the resultant solution was allowed to drop slowly into 300 ml. of ethanol. The red solution thus produced deposited crimson leaflets. Repetition of the solution-precipitation process afforded 4.0 g. (36%): m.p., 142° dec.

Anal. Calcd. for $C_{31}H_{23}Cl_2NO_8$: C, 64.59; H, 4.02; Cl, 12.32; N, 2.43. Found: C, 64.25; H, 4.29; Cl, 12.61, 12.72; N, 2.48.

Attempts to use several of the more conventional recrystallization techniques were unsuccessful, either achieving no purification or producing tar.

Reactions of Mannich products with acetic acid. In one experiment 0.10-g. samples of III, IV, V, and VIII were added to 2.5 ml. of glacial acetic acid and allowed to stand at room temperature. From III and IV there was obtained 0.05 g. (each), and from V and VIII there was obtained 0.06 g. (each) of I, which was identified by infrared spectrum and melting point. The order in which the original color was replaced by the yellow of I was IV > V > VIII > III. In a separate experiment VII was shown to change color more rapidly than III.

Reactions of Mannich products with acetic anhydride. In a typical experiment a small sample of the substituted aminomethyllawsone was added to 1 ml. of acetic anhydride containing 2 drops of concd. sulfuric acid. Upon being allowed to stand overnight a yellow precipitate appeared. This was identified by infrared spectrum and m.p. (235–237° dec.) as the diacetate of I. The authentic sample for comparison was prepared according to the directions of Fieser[6]: m.p. 235–237° dec., reported m.p., 132–133°.[12]

Anal. Calcd. for $C_{25}H_{16}O_8$: C, 67.57; H, 3.63. Found: C, 67.63; H, 3.72.

Reactions with acetaldehyde. A slight excess of the amine (0.007–0.008 mole) and 0.5 ml. of acetaldehyde was dissolved in 10 ml. of absolute ethanol and treated dropwise with a filtered solution of 1.0 g. (0.006 mole) of lawsone in 100 ml. of absolute ethanol by means of a Hershberg (slow addition) dropping funnel. Addition required 1 hr. The initial precipitate was suction filtered and washed well with 1:1 ethanol-ether and then vacuum dried. Data are collected in Table I. Appreciable additional quantities of less pure products were obtained in every case by evaporation or further dilution of mother-liquors with ether and/or petroleum ether.

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(12) This value is apparently erroneous and should be 232–233°. In order to confirm this, our synthetic product was analyzed.

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY, SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XXIX. 5-Diazoimidazole-4-carboxamide and 5-Diazo-*v*-triazole-4-carboxamide[1,2]

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Received October 19, 1960

The initial product of the diazotization of 5(or 4)-aminoimidazole-4-(or 5)-carboxamide has been isolated and shown to be 5-diazoimidazole-4-carboxamide. The diazo derivative, stable in the absence of moisture, cyclizes in aqueous solutions to the fused-ring isomer, 2-azahypoxanthine. 5-Diazo-*v*-triazole-4-carboxamide and 2,8-diazahypoxanthine have likewise been obtained from 5-amino-*v*-triazole-4-carboxamide. 5-Diazoimidazole-4-carboxamide has anticancer activity *in vitro* and *in vivo*. The structure of the diazoheterocycles is discussed.

The 2-azapurines (imidazo[4,5-*d*]-*v*-triazines) belong to the group of heterocyclic analogs of purines that have shown activity as inhibitors of neoplastic cells[3,4] and of microorganisms.[5] The few known 2-azapurines have been obtained by diazotization of the appropriate aminoimidazoles.[5–8] The reaction of 5(or 4)-aminoimidazole-4(or 5)-carboxamide (I) hydrochloride with sodium nitrite in aqueous solution has been reported to furnish 2-azahypoxanthine (imidazo[4,5-*d*]-*v*-triazin-4-(3*H*)-one) (III) directly in 85% yield.[5]

In the present work, a compound different from 2-azahypoxanthine has been obtained as the initial product of diazotization of 5(or 4)-aminoimidazole-4(or 5)-carboxamide (I) (AIC). The new compound forms, in yields of 70-94%, as a crystalline precipitate when a solution of AIC hydrochloride in 1*N* hydrochloric acid is added to an aqueous solution of sodium nitrite. The nature of the precipitate was first revealed by a positive Bratton-Marshall test,[9] indicative of an aromatic diazo group; by a sharp, intense infrared band—at 2190 cm.$^{-1}$—in the region characteristic of triple-bond and cumulative double-bond structures; and by analytical data in accord with the empirical formula $C_4H_3N_5O$. These and subsequent observations show that the initial product of the diazotization of AIC (I) is 5-diazoimidazole-4-carboxamide, which is represented here by the dipolar structure of

(1) The work described in this paper was presented before the Division of Medicinal Chemistry, 137th Meeting of the American Chemical Society, Cleveland, Ohio, April 5–14, 1960.

(2) This investigation was supported by the C. F. Kettering Foundation and the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. Sa-43-ph-1740.

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