CHEMOTHERAPY OF TUBERCULOSIS

Part III. Preparation of 5: 5′-Dichlorosalicil and Heterocyclic Derivatives from Dichlorosalicil and Related α-Diketones

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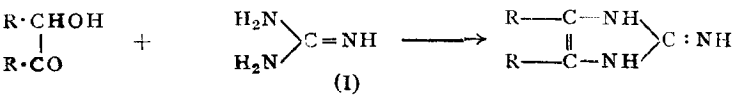
In the design and synthesis of compounds as possible cures for tuberculosis, we have been taking leads from the results and observations in diverse fields which suggest definite relationship between some structural features and high degree of bacteriostatic activity. In this context, the researches of Kuhn[1] attracted our attention. Following the discovery that 4: 4′-diaminobenzil is a powerful antagonist of *p*-aminobenzoic acid, Kuhn studied the effects of 4: 4′-dihydroxy-, 2: 2′-dihydroxy-, 2: 2′-dimethoxy-, and 5: 5′-dibromo-2: 2′-dihydroxy benzils and found that the last mentioned compound (" bromosalicil " or " 3065 ") was a powerful inhibitor of the growth of *Staphylococcus aureus in vitro.* Bromosalicil was claimed to rival penicillin in its bacteriostatic effects and to be very effective against sulphonamide-resistant gonorrhœa. Buu-Hoi[2] confirmed the antibacterial properties of bromosalicil and also announced that the chlorine analogue, chlorosalicil (*i.e.*, 2: 2′-dihydroxy-5: 5′-dichlorobenzil), was far superior to bromosalicil or the sulphonamides. With this as the background, we undertook to synthesise and study compounds related to and arising out of the benzils.

First, the study of the therapeutic action of chlorosalicil in plague infection gave rise to disappointment. Though chlorosalicil inhibited the growth of *P. pestis in vitro* in a dilution of 1: 500,000, it gave no protection to infected mice in tests conducted according to the method of Sokhey and Dikshit.[3] When the drug was fed to infected mice in doses of 10 mg. twice a day, the mice developed peripheral neuritis; under the reduced dosage levels of 1 mg., 2 mg., and 3 mg. twice a day, the compound gave no protection to the infected mice. The dimethylether of chlorosalicil also gave the same results as chlorosalicil. Thus, these compounds appear to be mere antiseptics rather than true chemotherapeuticals. This has been confirmed by Schales and Suthon[4] who have found that in spite of its powerful antibacterial activity *in vitro* and low toxicity, dibromosalicil was of little value in the treatment of systemic infections.

Next, in the anticipation that the modification of some of the structural features of chlorosalicil might lead to compounds behaving as true chemotherapeuticals, we have synthesised imidazole, hydantoin, quinoxaline and diurein derivatives starting from chlorosalicil. In addition to chlorosalicil other benzils, acyclic diketones and orthoquinone have also been employed to synthesise the abovementioned heterocyclic compounds. The compounds thus obtained are listed in the table. The compounds have been named in accordance with the nomenclature adopted in the " Chemical Abstracts ".

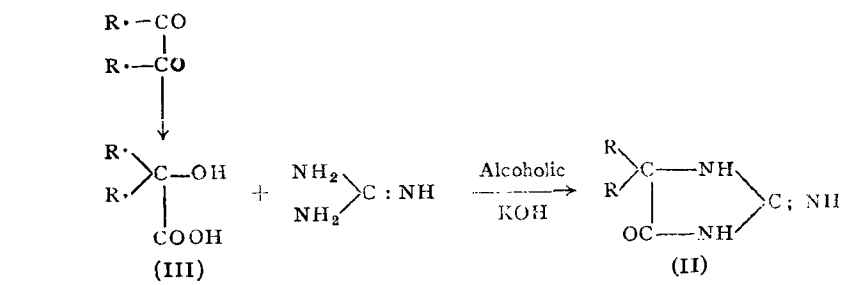
Starting from chlorosalicil dimethyl ether, the imidozolone (No. 51) was obtained by an adoptation of the method of Anschutz and Gelderman[5] and the diurein (No. 52) according to Angeli[6] and Biltz.[7] 5: 5′-Di-(2′-methoxy-5′-chloro)-phenyl hydantoin (No. 50), was obtained by heating chlorosaliciloin dimethylether with urea and alcoholic potash according to the procedure of Biltz and Rimpel.[8]

Attempts were made to synthesise the two interesting, and as yet unknown, groups of compounds, 4: 5-disubstituted imidazoloneimides and 5: 5-disubstituted-2-imidohydantoins. The synthesis of the 4: 5-diphenyl-imidozoloneimide (I) and its derivative by the action of guanidine on benzoin or chlorosaliciloin in acetic acid medium as follows was tried:

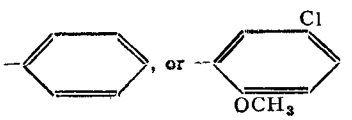


(I)

In spite of repeated attempts, the condensation would not go; the starting benzoin was recovered unchangd. On the other hand, the condensation of guanidine with benzil or the desired α-diketones in alcoholic potash furnished the desired 5: 5-disubstituted imidohydantoins (II). Conceivably,



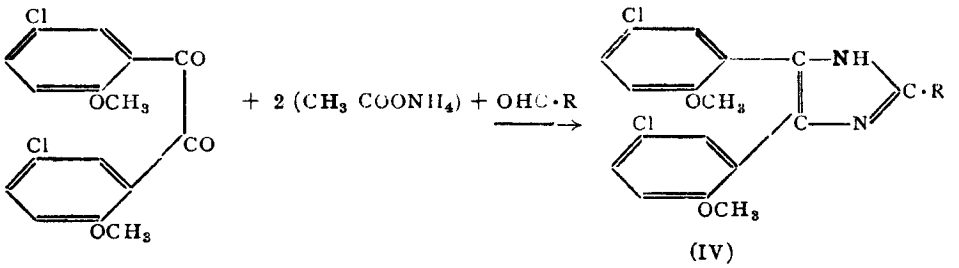
(III) (II)

where, R= 

the diketone undergoes benzil-benzilic acid rearrangement first and the benzilic acid derivative (III) so produced yields the product (II) on condensation with guanidine.

4: 5-Di-(2′-methoxy-5′-chloro)-phenylimidazole (No. 54), the substituted 2: 4: 5-triphenylimidazoles (Nos. 55–59, 63, 66, 69–73), and the 2-substituted 4: 5-dimethylimidazoles (Nos. 75 and 76) were synthesised by the method of Davidson, Weiss and Jetting.[9]

The synthesis of 2-alkyl and 2-alkylene derivatives of 4: 5-diphenylimidazole (IV) starting from chlorosalicil dimethylether was attempted as shown below:—



(IV)

(i) R= $-CH_2 \cdot CH_3$, $-(CH_2)_2 \cdot CH_3$ etc.
(ii) R= $-CH : CH \cdot CH_3$, $-CH : CH \cdot C_6H_5$

All efforts to synthesise compounds of type (IV) proved unsuccessful. Since benzil has been reported to react very easily with aliphatic aldehydes to furnish 2-alkyl-4: 5-diphenylimidazoles,[10] the failure in the present case is due to the decreased reactivity of the keto groups in chlorosalicil dimethyl-ether. This is supported by the fact that chlorosalicildimethyl-ether is colourless (*cf.* Robinson[11]). The result obtained in the case of unsaturated aldehydes is not surprising; even benzil does not react with these to yield imidozoles. On the other hand, formaldehyde and aromatic aldehydes are able to react even with chlorosalicil dimethylether to yield the corresponding imidazoles (Nos. 54–59, 63).

2-(2′-Hydroxy-5′-chloro)-phenyl-4 : 5-(9′–10′ phenanthra)-imidazole (No. 78) was obtained from 9: 10-phenanthraquinone according to the method of Cook and Jones.[10] However, β-naphthaquinone and 3: 4-phenanthraquinone did not undergo similar condensations with benzaldehyde derivatives in accordance with the observations of these authors so that this excellent method could be applied only to 9: 10-phenanthranequinone for such a synthesis. Though Cook and Jones[10] state that diacetyl cannot be used in imidazole synthesis, 2-substituted 4: 5-dimethylimidazoles (Nos. 75 and 76) have been easily synthesised from diacetyl. Bernhauer and

Benzils, α-Diketones and Heterocyclics derived from them

Serial No.	Name of the Compound	Molecular Formula	M.P./°C.	Nitrogen percentage	
				Found	Required
45	Chlorosaliciloin dimethyl ether		101–02		
46	Chlorosalicil (5:5-Dichlorosalicil)		197–98		
47	Chlorosalicil dimethyl ether		208–09		
48	2:2′-Dichlorobenzil		133–34		
49	Anisil		131–32		
50	5:5′-Di-(2′-methoxy-5′-chlorophenyl)-hydantoin	$C_{17}H_{14}O_4N_2Cl_2$	247–48	7·4	7·4
51	4:5-Di-(2′-methoxy-5′-chlorophenyl-)-imidozolone	$C_{17}H_{14}O_3N_2Cl_2$	215 onwards	7·1	7·7
52	Di-(2′-methoxy-5′-chlorophenyl)-acetylene diurein	$C_{18}H_{16}O_4N_4Cl_2$	310	13·2	13·2
53	5:5′-Di-(2′-methoxy-5′-chlorophenyl-)-2-imidohydantoin	$C_{17}H_{15}O_3N_3Cl_2$	297–98	11·1	11·1
54	4:5-Di-(2′-methoxy-5′-chlorophenyl-) imidazole	$C_{17}H_{14}O_2N_2Cl_2$	212–13	8·4	8·1
55	2-(2′-Hydroxy-) phenyl-4:5 di-(2′-methoxy-5′-chlorophenyl-) imidazole	$C_{23}H_{18}O_3N_2Cl_2$	236–58	5·8	6·3
56	2-(4′-Hydroxy-) phenyl-4:5-di-(2′ methoxy-5′-chlorophenyl-) imidazole	$C_{23}H_{18}O_3N_2Cl_2$	250–51	6·2	6·3
57	2′:2′:2′-Trimethoxy-5′:5′:5′-trichlorolophine	$C_{24}H_{19}O_3N_2Cl_3$	201–02	5·8	5·7
58	2-(2′-Hydroxy-5′-chloro)-phenyl-4:5 (2′-methoxy-5′-chlorophenyl-) imidazole	$C_{23}H_{17}O_3N_2Cl_2$	245–48	5·3	5·9
59	2-(4′-Dimethylamino-) phenyl-4:5-di-(2′-methoxy-5′-chlorophenyl-) imidazole	$C_{25}H_{23}O_2N_3Cl_2$	256–57	8·3	8·9
60	2:3-Di-(2′-methoxy-5′-chlorophenyl-)-4:5-dihydropyrazine	$C_{18}H_{16}O_2N_2Cl_2$	161–62	7·5	7·7
61	6-Methyl-2:3-di-(2′-methoxy-5′ chlorophenyl-) quinoxaline	$C_{23}H_{18}O_2N_2Cl_2$	165–66	6·4	6·6
62	6-Chloro-2:3-di-(2′-methoxy-5′-chlorophenyl-) quinoxaline	$C_{22}H_{15}O_2N_2Cl_3$	188–90	6·1	6·3
63	2′:2:2′-Trihydroxy-5′:5′:5′-trichlorolophine	$C_{21}H_{13}O_3N_2Cl_3$	255–56	6·2	6·3
64	2:3-Di-(2′-hydroxy-5′-chlorophenyl-) quinoxaline	$C_{20}H_{12}O_2N_2Cl_4$	215–16	7·5	7·3
65	6-chloro-2:3-di-(2′-hydroxy-5′-chlorophenyl-) quinoxaline	$C_{20}H_{11}O_2N_2Cl_3$	198–99	6·8	6·7
66	2-(4′-Hydroxy-) phenyl-4:5-diphenyl imidazole	$C_{21}H_{16}ON_2$	256–58	8·4	8·9
67	5:5-Diphenyl-2-imidohydantoin	$C_{15}H_{13}ON_3$	305	16·0	16·7
68	6-Chloro-2:3-diphenyl-quinoxaline	$C_{20}H_{13}N_2Cl$	123–24 lit.[19], 130	8·8	8·8
69	2-(2′-Methoxy-5′-chloro-) phenyl-4:5-diphenyl imidazole	$C_{22}H_{17}ON_2Cl$	215–16	7·7	7·8
70	2-(2′-Hydroxy-5′-chloro-) phenyl-4:5-diphenyl imidazole	$C_{21}H_{15}ON_2Cl$	191–92	8·1	8·1
71	2-(2′:-Bromo-5′hydroxy-) phenyl-4:-5-diphenyl imidazole	$C_{21}H_{15}ON_2Br$.	110– (dec.)	6·7	7·2

Serial No.	Name of the Compound	Molecular Formula	M.P./°C.	Nitrogen percentage	
				Found	Required
72	2-(2'-Hydroxy-5'-chlorophenyl-) 4:5-di-(4'-methoxyphenyl-) imidazole	$C_{23}H_{19}O_3N_2Cl$	163–65	6·5	6·9
73	2-(2'-Hydroxy-5'-chlorophenyl-)-4:5-di-(2'-chlorophenyl-) imidazole	$C_{21}H_{14}ON_2Cl_3$	219–20	6·4	6·7
74	6-Chloro-2:3-di-(2'-chlorophenyl-) quinozaline	$C_{20}H_{11}N_2Cl_3$	123–24	7·4	7·3
75	2-(2'-Hydroxy-5'-chlorophenyl-)-4:5-dimethyl imidazole	$C_{11}H_{12}ON_2Cl$	254–55	12·0	12·5
76	2-(4'-Dimethylaminophenyl-)-4:5-dimethyl imidazole)	$C_{13}H_{17}N_3$	264–74	18·9	19·5
77	6-Chloro-2:3-dimethyl quinoxaline	$C_{10}H_9N_2Cl$	91–92	14·4	14·6
78	2-(2'-Hydroxy-5'-chlorophenyl-)-4:5-(9':10'-phenanthra-) imidazole	$C_{21}H_{13}ON_2Cl$	246–48	7·5	8·1

Hoffmann[12] have observed that at least small amounts of 2-phenyl-4:5-dimethylimidazole are formed by the action of acetoin, benzaldehyde and ammonia in the presence of copper acetate.

The dihydropyrazine derivative (No. 60) and the benzopyrazine or quinoxaline compounds (Nos. 61, 62, 64, 65, 68, 74 and 77) were obtained without difficulty by the use of the customary methods available in literature.

Four representative compounds of the series (Nos. 60, 63, 65 and 75) were tested for their toxicity and also for their therapeutic effect in experimental plague infections in mice according to the technique of Sokhey and Dikshit.[3] In the toxicity tests, the compounds were fed to groups of mice in graded doses of 5, 20 and 40 mg. once a day for two days, followed by giving the dose twice a day for the next two days. In the case of drug No. 65, two out of five mice died at the 40 mg. dosage schedule. Drug No. 75 was lethal to mice even in the lowest dosage level tried and so was excluded from actual testing in experimental plague infection.

In chemotherapeutic trials, the three drugs (Nos. 60, 63 and 65) were fed at the standard dose level of 10 mg. twice a day for seven days, starting the treatment 32 hours after infection. None of the drugs showed any protective action.

Since results in plague and tuberculosis need not necessarily correspond, all the compounds reported here are being tested for their action against the tubercle bacilli.

Experimental

5-Chlorosalicylaldehyde methylether.—This compound was obtained by the methylation of 5-chlorosalicylaldehyde[13] utilising the convenient preparative method of Barget and Silberschmidt[14] as adopted by Buck[15] for the preparation of veratraldehyde.

5-Chlorosalicylaldehyde (104 g., 1 mol.), contained in a 500 c.c. three-necked flask fitted with a stirrer and two separating funnels, was melted under stirring in an oil-bath at 110–20° C. Potassium hydroxide (62 g., 1·5 mols.) in water (100 c.c.) and freshly purified dimethyl sulphate (80 c.c., 1·25 mols.) were simultaneously run into the melt at about the same rate, after removal of the external source of heat. The entire operation was finished in about 10–15 minutes. Stirring was, however, continued for further 15 minutes. The hot reaction mixture was poured into a 400 c.c. beaker and, while cooling, was stirred with a rod till granules of the methyl ether are mostly deposited, and allowed to stand overnight. The white crystalline aldehyde was filtered, washed and dried between filter-papers (108 g., m.p. 77–79°).

5-Chlorosalicylaldehyde methyl ether thus obtained separates from alcohol in colourless needles, m.p. 79–80° (Buu-Hoi[2] reports m.p. 81°), yield 106 g.

2 : 2'-Dimethoxy-5 : 5'-dichlorobenzoin, or "*chlorosaliciloin dimethyl ether*".—This was prepared by adoption of the process of Adams and Marvel[16] for benzoin.

A mixture of 2-methoxy-5-chlorobenzaldehyde (50 g., m.p. 79–80°), alcohol (65 c.c.), water (50 c.c.), and sodium cyanide (5 g.) were gently refluxed till a violent reaction set in (5–10 minutes). External heat was removed and the mixture allowed to stand. The resulting benzoin was filtered when cold, and washed with 50 per cent. alcohol (200 c.c.) on the filter when it remained as a white crystalline product (m.p. 101–02°; yield, 35 g.). It was of a high order of purity and could be used directly for oxidation to chlorosalicil dimethyl ether.

Chlorosaliciloin separates from alcohol in colourless needles, m.p. 101-02°. The melting point of this compound is not mentioned in literature.

2 : 2'-Dimethoxy-5 : 5'-dichlorobenzil, or "*chlorosalicil dimethyl ether*".—This was obtained by use of the directions of Clarke and Dredger[17] for benzil.

In a 1 l. two-necked flask, fitted with a reflux condenser and an air inlet tube were placed copper sulphate (82 g.), pyridine (160 c.c.) and water

(40 c.c.) and the mixture heated on the water-bath till most of the copper sulphate had dissolved. Chlorosaliciloin dimethyl ether (45 g.) was then added and the mixture heated at 100° for 2 hours, while a current of compressed air was being passed in. The mixture was thereafter cooled, filtered and the solid washed with water till free of copper salt (disappearance of blue colour).

Chlorosalicil dimethyl ether separates from alcohol in colourless needles, m.p. 208–09° (literature[2] records, m.p. 209°); yield, 44·3 g.

Chlorosalicil.—A mixture of chlorosalicil dimethyl ether (35 g.), chlorobenzene (175 c.c.) and anhydrous aluminium chloride (350 g.), protected from atmospheric moisture, was heated at 60° under reflux with frequent shaking for 7 hours. The mixture was cooled and poured into an excess of dilute hydrochloric acid and crushed ice. The chlorobenzene was tapped off and the aqueous solution repeatedly extracted with chlorobenzene. The pooled chlorobenzene extract was washed with water and subsequently exhausted with dilute sodium hydroxide. The yellow fluorescent alkaline solution, on acidification, yielded the desired chlorosalicil which crystallised from alcohol in greenish yellow needles, m.p. 196–97° (agreeing well with a m.p. of 197° recorded by Buu-Hoi for a specimen crystallised from acetic acid); yield, 16 g.

Anisil and 2:2′-*dichlorobenzil* were prepared by methods similar to that described for chlorosalicil dimethyl ether.

During the preparation of 2:2′-dichlorobenzil, the intermediate benzoin could not be isolated in the solid state. The oil that was obtained was washed with dilute alkali and oxidised by means of air in the presence of copper sulphate, and pyridine. From 79 g. of *o*-chlorobenzildehyde were obtained 35 g. of 2:2′-dichlorobenzil as greenish yellow needles from alcohol, melting at 133°.

2:2′-Dichlorobenzil has been previously prepared according to a different method by Hodgson and Rosenberg[18] who report a melting point of 128° for the diketone.

4: 5-*Di*-(2′-*methoxy*-5′-*chloro*)-*phenylimidazolone* (*No.* 51).—Chlorosaliciloin dimethyl ether (6 g.), urea (2 g.) and acetic acid (100 c.c.) were heated together under reflux for 1 hour, the solution filtered and diluted to turbidity with hot water. The imidazolone was collected and crystallised from acetone; it was obtained in colourless needles; yield, 3 g.

Di-(2′-*methoxy*-5′-*chloro*)-*phenylacetylenediurein* (*No.* 52).—A mixture of chlorosalicil dimethyl ether (5 g.) and urea (19 g.) was heated in a conical

flask at 220° in an oil-bath for 20 minutes. The product was extracted 4 times with 1 l. lots of boiling water, washed with cold dilute sodium hydroxide and then with water. The acetylene diurein separated from acetic acid in faint yellow needles; yield, 2·5 g.

5: 5-*Di*-(2'-*methoxy*-5'-*chloro*)-*phenylhydantoin* (*No.* 50).—A mixture of chlorosalicil dimethyl ether (5 g.), urea (2 g.) in alcohol (75 c.c.) and saturated potassium hydroxide solution (12 c.c.) was refluxed for 2 hours and then diluted with excess of water. The solution was decolorised (charcoal), and acidified with hydrochloric acid. The resulting hydantoin crystallised from alcohol-acetic acid in colourless needles, m.p. 247–48°; yield, 3·4 g.

5: 5-*Di*-(2'-*methoxy*-5'-*chloro*)-*phenyl*-2-*imidohydantoin* (*No.* 53).—A mixture of chlorosalicil dimethyl ether (5 g.), guanidine nitrate (5 g.), potassium hydroxide (25 c.c. of 50 per cent.) and alcohol (100 c.c.) was refluxed for 2 hours, filtered and acidified with acetic acid. The imidohydantoin separated from alcohol-acetic acid in colourless prismatic needles, m.p. 297–98°; yield, 4·3 g.

5-5'-*Diphenyl*-2-*imidohydantoin* (*No.* 67).—Benzil (10 g.), guanidine nitrate (10 g.), 50 per cent. potassium hydroxide (50 c.c.) and alcohol (200 c.c.) were treated together under reflux for 2 hours and worked up as above in the previous experiment. The desired 2-imidohydantoin crystallised from alcohol in colourless, prismatic needles, m.p. 305°; yield, 10·6 g.

4: 5-*Di*-(2'-*methoxy*-5'-*chloro*)-*phenyl imidazole* (*No.* 54).—A solution of chlorosalicil dimethyl ether (5 g.), urotropine (0·42 g.), ammonium acetate (10 g.) in acetic acid (75 c.c.) was refluxed for 1 hour, and diluted to turbidity with hot water. The imidazole, which separated out on cooling with some unchanged diketone, was collected and fractionally crystallised from alcohol. The later fraction, which consisted of faint yellow crystals, were collected and constituted the required imidazole, m.p. 211–13°; yield, 1·5 g.

The 2: 4: 5-*triphenyl imidazoles* (*Nos.* 55–59, 63, 66, 69–73)—were prepared from the relevant α-diketones or benzaldehydes and ammonium acetate in the presence of acetic acid according to the method of Davidson, *et al.*[9] as worked out for the case of lophine. They were invariably obtained in a high state of purity and in yields ranging from 85–100 per cent. The method adopted is exemplified in the preparation of the first member of the series, *viz.*, Compound No. 55.

2-(*o*-*Hydroxy*)-*phenyl*-4 : 5-*di*-(2'-*methoxy*-5'-*chloro*)-*phenyl imidazole* (*No.* 55).—Chlorosalicil dimethyl ether (3·39 g.), salicylaldehyde (1·1 c.c., 1 mol.), ammonium acetate (8 g.) and acetic acid (50 c.c.) were refluxed

together for 1 hour. The hot solution was charcoaled, filtered and diluted with water to turbidity. The imidazole, which separated out on cooling, was collected and on recrystallisation from alcohol it separated in faint yellow needles, m.p. 236–38°; yield, 4·0 g.

The *2-substituted-4-5-dimethyl imidazoles* (*Nos.* 75 *and* 76)—were obtained, like the triphenyl imidazoles, by the reaction of diacetyl with the appropriate aldehyde and ammonium acetate in acetic acid solution. These compounds were distinctly basic and did not therefore separate out on dilution of the reaction mixture, but were easily obtained by basification with ammonium hydroxide. Whereas the yield of No. 75 was about 91 per cent. of theory, 2-(*p*-dimethylamino-)-phenyl-4: 5-dimethylamidozol (No. 76) could be isolated only in moderate yields of 25–30 per cent.

2-(2'-Hydroxy-5'-chloro-)-phenyl-4: 5-(9': 10'-phenanthra-)-imidazole (*No.* 78).—9: 10-Phenanthraquinone (5·2 g.), chlorosalicilaldehyde (3·41 g.) and ammonium acetate (15 g.) were brought together in acetic acid (75 c.c.). Within a few minutes, the clear red solution deposited bright yellow needles presumably of the imidazole. However, the mixture was heated for 1 hour after adding further amount of acetic acid (25 c.c.). The phenanthraimidazole on recrystallisation from alcohol was obtained as colourless needles, m.p. 247–48°; yield, 6·9 g.

2: 3-Di-(2'-methoxy-5'-chloro-)-phenyl-4 : 5-dihydropyrazine (*No.* 60).—Chlorosalicil dimethyl ether (3·1 g.) and ethylenediamine (0·5 g.) were brought together in alcohol (20 c.c.), refluxed for 1 hour, charcoaled, filtered and the solution diluted to turbidity with water. The dihydropyrazine crystallised from alcohol in colourless needles, m.p. 161–62, yield, 3·5 g.

The *quinoxalines* (*Nos.* 61, 62, 64, 65, 68, 74 and 77)—were formed in nearly quantitative yields when the appropriate diketone was reacted with the relevant phenylenediamine in alcohol or alcohol-acetic acid mixture by heating for 1 hour. Many of them were produced rapidly even at room temperature.

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Summary

The highly favourable first reports about the antibacterial merits of 5: 5'-dihalogenated salicils and the essentially sulphonamide-like nature of their action on bacteria, led to an improved method of preparation of 5: 5'-

dichlorosalicil or " chlorosalicil " for ascertaining its usefulness in human tuberculosis.

The ineffectiveness of chlorosalicil on *P. pestis in vivo* directed attention to the synthesis of a series of biologically interesting heterocyclic ring-systems, particularly the imidazole and pyrazine types, starting with chlorosalicil, benzil, 2:2′-dichlorobenzil, anisil, diacetyl and *ortho*quinones, regarded as cyclic α-diketones.

A total of twenty-eight heterocyclic compounds have been synthesised in this connection. Synthesis of these furnished interesting information regarding the chemistry of imidazoles.

A few representative heterocyclics, now prepared, have been subjected to examination for efficacy *in vivo* against *P. pestis*, which definitely demonstrated reduction of the original toxicity for infected mice of the initial α-diketones following heterocyclic synthesis from the ketones. However these failed to exhibit any curative action. The failure in experimental plague of the compounds studied has not yet been correlated with their possible anti-mycobacterial activities.

References

1. Kuhn, Birkhofer and Moller .. *Ber.*, 1943, **76 B**, 900; *Extract from the Combined Intelligence Objectives Sub-Committee*, C. 108. Target 18158, J. 1945, 4 M.
2. Buu-Hoi .. *Compt. rend.*, 1945, **221**, 202.
3. Sokhey and Dikshit .. *Lancet*, 1940, **1**, 1040.
4. Suthon .. *Arch. Biochem.*, 1946, **11**, 397.
5. Anschutz and Gelderman .. *Ann.*, 1891, **261**, 129.
6. Angeli .. *Gaz.*, 1899, **19**, 563.
7. Biltz .. *Ber.*, 1907, **40**, 4799, 4806.
8. ——— and Rimpel .. *Ibid.*, 1908, **41**, 1379.
9. Davidson, Weiss and Jetting .. *J. Org. Chem.*, 1937, **2**, 319.
10. Cook and Jones .. *J. Chem. Soc.*, 1941, 278.
11. Robinson, R. .. *Two Lectures* (*Institute of Chemistry*), 1932, **31**.
12. Bernhauer and Hoffmann .. *J. Prakt. Chem.*, 1937, **149**, 323.
13. Biltz and Stoff .. *Ber.*, 1905, **37**, 4024.
14. Barget and Silberschmidt .. *J. Chem. Soc.*, 1928, **133**, 2924.
15. Buck .. *Org. Synth.*, 1943, Coll., **2**, 619.
16. Adams and Marvel .. *Ibid.*, 1932, Coll., **1**, 88.
17. Clarke and Dredger .. *Ibid.*, 1932, Coll., **1**, 80.
18. Hodgson and Rosenberg .. *J. Chem. Soc.*, 1930, 14.
19. Fischer and Limmer .. *J. Prakt. Chim.*, **74** (2), 60.