g. of cyanogen bromide and 67 g. of 6-chlorotetrahydroquinoline. The yield of purified material boiling at 155° (2 mm.) and melting at 54–55° was 44%.

Anal. Calcd. for $C_{16}H_{13}ClN_2$: N, 14.53. Found: N, 14.43.

1-(*p*-Nitrophenylguanyl)-1,2,3,4-tetrahydroquinoline.—N-Cyanotetrahydroquinoline (13.0 g., 0.082 mole) and *p*-nitroaniline hydrochloride (14.3 g., 0.082 mole) were heated in the absence of a solvent by means of an oil-bath, the temperature being slowly raised to 200° (bath temperature). The resulting red solid was dissolved in 180 cc. of hot alcohol, poured into 200 cc. of water containing 8 g. of sodium hydroxide, and the solid material (24.9 g., m.p. 155–169°) which separated was removed by filtration. After crystallization once from 800 cc. of alcohol and once from 800 cc. of acetone, the material (9.1 g., m.p. 176.5–179.5°) was extracted with 600 cc. of boiling dioxane leaving a small residue melting from 162° to 275°. The dioxane solution was concentrated to 160 cc. and water was added to a faint turbidity while hot. On chilling 6.3 g. of an orange yellow solid melting at 187.5–188.5° was obtained. An additional 3.6 g. of less pure product (m.p. 183.5–187°) was recovered from the mother liquors.

Anal. Calcd. for $C_{16}H_{16}N_4O_2$: C, 64.83; H, 5.44; N, 18.91. Found: C, 64.78; H, 5.62; N, 18.88.

1-(*p*-Methoxyphenylguanyl)-1,2,3,4-tetrahydroquinoline hydrochloride was prepared similarly from 11.1 g. of N-cyanotetrahydroquinoline and 11.1 g. of *p*-anisidine hydrochloride. The substance was precipitated from an ether solution with hydrogen chloride and recrystallized three times from alcohol–ether to give 3.4 g. (15%) of white crystals melting at 185–186°.

Anal. Calcd. for $C_{17}H_{20}ClN_3O$: C, 64.10; H, 6.34; Cl, 11.16. Found: C, 64.10; H, 6.35; Cl, 11.13.

Bis-(1,2,3,4-tetrahydroquinolyl-1)-ketimine was prepared in 57% yield from 16.5 g. of cyanotetrahydroquinoline and 22.7 g. of tetrahydroquinoline hydrobromide in the absence of a solvent at 160°. Crystallization from alcohol–petroleum ether formed a white microcrystalline powder melting at 146.5–147.5°.

Anal. Calcd. for $C_{19}H_{21}N_3$: C, 78.31; H, 7.27; N, 14.42. Found: C, 78.35; H, 7.40; N, 14.62.

Bis-(6-methoxy-1,2,3,4-tetrahydroquinolyl-1)-ketimine was prepared as in the previous reaction from 9.8 g. of thalline hydrobromide and 7.5 g. of N-cyanothalline. Crystallization from aqueous alcohol gave a 23% yield of a white powder melting at 143.5–143.8°.

Anal. Calcd. for $C_{21}H_{25}N_3O_2$: C, 71.77; H, 7.67; N, 11.96; CH_3O, 17.67. Found: C, 71.62; H, 7.31; N, 12.21; CH_3O, 17.93.

1-(*p*-Nitrophenylguanyl)-6-methoxy-1,2,3,4-tetrahydroquinoline.—Seven grams of *p*-nitroaniline hydrochloride and 7.5 g. of N-cyanothalline treated as in the previous reaction gave a 23% yield of deep red crystals (from alcohol) melting at 132.5–134°.

Anal. Calcd. for $C_{17}H_{19}N_4O_3$: C, 62.62; H, 5.56; N, 17.17; CH_3O, 9.51. Found: C, 62.92; H, 5.68; N, 17.08; CH_3O, 10.08.

1-(1-Chlorophenylguanyl)-6-methoxy-1,2,3,4-tetrahydroquinoline.—Analogously, 13.1 g. of *p*-chloroaniline hydrochloride and 15.0 g. of N-cyanothalline formed 17.5% of white crystals melting (after crystallization from ethyl acetate) at 135.5–136.5°.

Anal. Calcd. for $C_{17}H_{18}ClN_3O$: C, 64.65; H, 5.74; N, 13.31; CH_3O, 10.2. Found: C, 64.81; H, 5.49; N, 13.96; CH_3O, 10.2.

1-Diethylguanyl-6-chlorotetrahydroquinoline Hydrochloride.—Seven grams of 6-chlorotetrahydroquinoline hydrochloride and 3.4 g. of diethylcyanamide were heated in absence of a solvent. At about 100°, an exothermic reaction took place, the temperature rising spontaneously to 165°. The melt was dissolved in water, adjusted to a *p*H of 8.5 and extracted (ether) to remove tetrahydroquinoline. The aqueous layer was made strongly basic and extracted thoroughly with ether after drying, dry hydrogen chloride was pressed through the solution to precipitate the hydrochloride (1 g.) which was crystallized to constant melting point, 207–210°, from ethyl acetate.

Anal. Calcd. for $C_{14}H_{21}Cl_2N_3$: C, 55.6; H, 6.96; N, 13.9. Found: C, 55.8; H, 6.73; N, 13.8.

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Reactions of Some Amines with Heterocyclic Ethers

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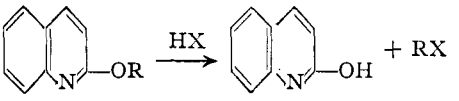
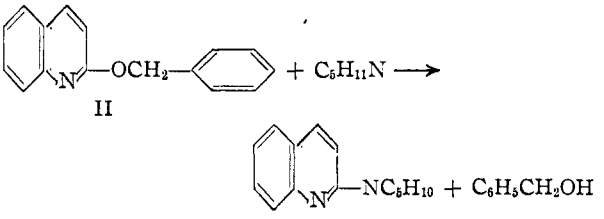
It has been shown that alkoxy groupings in the 2-position of quinoline are labile to reagents like hydrochloric acid,[1] thiophenols[2] and carboxylic acids.[3] The cleavage results in the formation of 2-hydroxyquinoline (I) and the alkylated cleaving reagent.



I X = Cl-, C_6H_5S-, RCOO-

These reactions suggested the possibility that 2-alkoxyquinolines might be cleaved by compounds containing the =NH grouping. Consequently in this work we have investigated the reactions between 2-benzyloxyquinoline (II) and certain aliphatic amines, aromatic amines and amides.

The aromatic amines, aniline, N-methylaniline, diphenylamine, carbazole and phenothiazine, reacted at relatively high temperatures like the acidic reagents to yield I and the alkylated amine. The aliphatic amines, piperidine and morpholine, showed this same cleavage at lower temperatures (boiling points of the amines). In addition, these cyclic aliphatic amines effected cleavage between the quinoline ring and the oxygen atom to yield the 2-aminoquinoline and benzyl alcohol. Dibenzylamine, acetanilide and N-benzylbenzenesulfonamide showed neither type of cleavage.



II

The reaction was also affected by the alkyl grouping, for experiments with diphenylamine and morpholine indicated that II was more reactive than 2-ethoxyquinoline. 2-Benzyloxybenzothiazole[3] did not react with diphenylamine at 115–125°.

Since phenothiazine reacted with II to form I in 90% yield, the other product which melted at 91–92° was thought to be N-benzylphenothiazine. The melting point corresponded with that reported by Desai[4] for N-benzylphenothiazine, but we were unable to prepare the compound by his method of heating sulfur and N-benzyldiphenylamine.

Finzi[5] reported a melting point of 132–134°

(1) P. Friedländer and H. Ostermaier, *Ber.*, **15**, 333 (1882).
(2) G. Illuminati and H. Gilman, THIS JOURNAL, **71**, 3349 (1949).
(3) H. Gilman, K. E. Lentz and J. A. Beel, *ibid.*, **74**, 1081 (1952).
(4) R. D. Desai, *J. Ind. Inst. Sci.*, **7**, 235 (1924).
(5) C. Finzi, *Gazz. chim. ital.*, **62**, 175 (1932).

TABLE I

REACTIONS OF N-HETEROCYCLIC ETHERS WITH —NH COMPOUNDS

Cleaving reagent	Reaction time, hr.	T., °C. (bath)	Products, %	Recovery of starting material, %
		Ether, 2-benzyloxyquinoline[a]		
Sodium hydroxide, aq. (20%)	7	Reflux	.....	2-Benzyloxyquinoline,[b] 94
Hydrochloric acid (6 *N*)	7	Reflux	2-Hydroxyquinoline,[c] 90 Benzyl chloride,[d] 46	.....
Aniline	48	170–180	2-Hydroxyquinoline,[c] 14 N-Benzylaniline,[e] 8	2-Benzyloxyquinoline,[b] 82 Aniline,[f] 62
N-Methylaniline	40	170–180	2-Hydroxyquinoline,[c] 76 N-Methyl-N-benzylaniline,[g] 41	.....
Diphenylamine	40	170–180	2-Hydroxyquinoline,[c] 84 N-Benzyldiphenylamine,[h] 58	Diphenylamine,[i] 58
Diphenylamine	48	100	No 2-hydroxyquinoline	.....
Diphenylamine	49	140[j]	No 2-hydroxyquinoline	.....
Carbazole	48	200–220[k]	2-Hydroxyquinoline,[c] 9.5	.....
Carbazole	48	140[j]	.....	Carbazole,[i] 93 2-Benzyloxyquinoline,[b] 88
Carbazole	48	165[l]	2-Hydroxyquinoline,[c] 16 N-Benzylcarbazole,[m] 7	Carbazole,[i] 80
Phenothiazine	48	170–210	2-Hydroxyquinoline,[c] 24	2-Benzyloxyquinoline,[b] 25
Phenothiazine	48	153[n]	2-Hydroxyquinoline,[c] 90 N-Benzylphenothiazine,[o] 34 (?)	.....
Di-*n*-butylamine	48	170–180	.....	Di-*n*-butylamine,[p] 76 2-Benzyloxyquinoline,[b] 84
Di-*n*-butylamine	48	170–180	2-Hydroxyquinoline,[c] 5	Di-*n*-butylamine,[p] 70 2-Benzyloxyquinoline,[b] 77
Dibenzylamine	48	180	.....	Dibenzylamine,[q] 53 2-Benzyloxyquinoline,[b] 66
Piperidine	46	Reflux	2-Hydroxyquinoline,[c] 15 N-Benzylpiperidine,[r] 22	.....
Piperidine	53	Reflux	2-Hydroxyquinoline,[c] 7 N-Benzylpiperidine,[r] 18 2-(N-Piperidino)-quinoline,[s] 2.5	2-Benzyloxyquinoline,[b] 76
Morpholine	53	Reflux	2-Hydroxyquinoline,[c] 35 N-Benzylmorpholine,[t] 19 Benzyl alcohol,[u] 28 2-(N-Morpholino)-quinoline,[v] 65	.....
Pyrrole	46	Reflux	.....	2-Benzyloxyquinoline,[b] 85
Acetanilide	48	125	.....	Acetanilide,[i] 82 2-Benzyloxyquinoline,[b] 62
N-Benzylbenzenesulfonamide	46	170	.....	2-Benzyloxyquinoline,[b] 70 N-Benzylbenzenesulfonamide,[i] 59
		Ether, 2-benzyloxybenzothiazole[w]		
Diphenylamine	26	115–125	.....	Diphenylamine,[i] 92 2-Benzyloxybenzothiazole,[x] 60
		Ether, 2-Ethoxyquinoline[y]		
Diphenylamine	48	170–180	.....	Diphenylamine,[i] 84 2-Ethoxyquinoline,[i] 82
Morpholine	48	Reflux	2-(N-Morpholino)-quinoline,[v] 3.4	Morpholine,[z] 94 2-Ethoxyquinoline,[i] 69

[a] See ref. 2. [b] M.p. 50°. Identified by mixed m.p. [c] M.p. 199°. Identified by mixed m.p. [d] B.p. 175–185°. Liquid gave a white precipitate with alc. silver nitrate. [e] Identified by m.p. (114–115°) of benzenesulfonamide and mixed m.p. [f] Converted to acetanilide and identified by mixed m.p. [g] Identified by m.p. (127–128°) of picrate and mixed m.p. See E. Wedekind, *Ber.*, **32,** 517 (1899). [h] Identified by m.p. (83.5–86.5°) and mixed m.p. See J. Forrest, D. A. Liddell and S. H. Tucker, *J. Chem. Soc.*, 454 (1946). [i] Identified by m.p. and mixed m.p. [j] Refluxed in xylene solution. [k] Extensive pyrolysis occurred. [l] Refluxed in mesitylene solution. [m] Identified by m.p. (117–119°) and mixed m.p. See B. Levy, *Monatsh.*, **33,** 177 (1912). [n] Refluxed in cumene solution. [o] M.p. 91–92°. *Anal.* Calcd. for $C_{19}H_{15}NS$: S, 11.1. Found: S, 10.7, 11.1. See refs. 4, 5. [p] Identified by m.p. (84–86°) of phenylthiourea and mixed m.p. [q] Isolated as N,N-dibenzylbenzamide (m.p. 112–114°) and identified by mixed m.p. [r] Identified by m.p. of the hydrochloride (m.p. 171–175°) and of the picrate (181°) and mixed m.p. See C. Schotten, *Ber.*, **15,** 421 (1882). [s] Identified by m.p. (174°) of the picrate and mixed m.p. See N. Luthy, F. W. Bergstrom and H. S. Mosher, THIS JOURNAL, **71,** 1109 (1949). [t] Identified by m.p. of hydrochloride (244–245°) and picrate (189–190°). See S. Gabriel and R. Stelzner, *Ber.*, **29,** 2381 (1896), Cerkovnikov and Stern, *Arkiv Kemi*, **18,** 12 (1946) [*C.A.*, **42,** 1942 (1948)], and J. P. Mason and M. Zief, THIS JOURNAL, **62,** 1450 (1940). [u] Converted to the α-naphthyl urethan (m.p. 132–133°) and identified by mixed m.p. [v] Identified by m.p. (91–92°) and mixed m.p. See L. Fullhart, Doctoral Dissertation, Iowa State College (1946). [w] See ref. 3. [x] Identified by m.p. (60–63°) and mixed m.p. [y] See ref. 1. [z] Converted to phenylthiourea (m.p. 132–134°) and identified by mixed m.p.

for the same compound which he prepared by heating benzyl chloride with phenothiazine. This compound was shown to be different from that obtained in our experiment by a mixed melting point determination. We were also unable to prepare N-benzylphenothiazine from N-lithiophenothiazine and benzyl chloride.

Experimental

In most of the experiments the reagents were stirred for 48 hours in a nitrogen atmosphere at a bath temperature of 170–180°. After cooling the mixture was shaken with ether, which precipitated most of the 2-hydroxyquinoline if it were present in appreciable amounts. The ether was then extracted with 5% aqueous sodium hydroxide to remove any residual 2-hydroxyquinoline which was recovered by acidification of these extracts with hydrochloric acid and concentration by evaporation. The ether layer was dried over sodium sulfate, and after filtration the ether was removed by distillation. From the residue the other cleavage products and unreacted starting materials were obtained by vacuum distillation or by recrystallization. In Table I we have listed the pertinent data for the various experiments.

Attempt to Prepare N-Benzylphenothiazine.—N-Lithiophenothiazine was prepared by adding 0.11 mole of phenyllithium in 20 ml. of dry ether to 5.0 g. (0.025 mole) of phenothiazine in 200 ml. of dry benzene. As this mixture gave a blue-green color which resembled Color Test I,[6] the time at which the phenyllithium was used up could not be noted, so the mixture was stirred at room temperature for 48 hours. A solution of 4.0 g. (0.03 mole) of benzyl chloride in 75 ml. of dry ether was then added, and the stirring was continued at room temperature for 24 hours. After refluxing for one hour, the volatile solvents were removed by distillation. This left a gummy residue which was extracted with 95% ethanol. No crystalline material could be obtained from these extracts.

Preparation of N-Benzylbenzenesulfonamide.—A modification of Hinsberg's method[7] was used in this preparation. The addition of 17.6 g. (0.1 mole) of benzenesulfonyl chloride and 40 ml. of 10% sodium hydroxide in small portions, with shaking, to 10.7 g. (0.1 mole) of benzylamine resulted in a brown oil. The mixture was shaken with an additional 400 ml. of 10% sodium hydroxide before filtering. After standing for two days it was filtered again and then acidified with hydrochloric acid. This yielded a white precipitate which was washed with water and dried. The yield was 17.3 g. (70%) of N-benzylbenzenesulfonamide (m.p. 87–89°). Attempts to recrystallize the material from aqueous ethanol, as recommended by Hinsberg, yielded a tan material with a lower melting point (about 80°).

Acknowledgment.—The authors are grateful to Dr. Gabriello Illuminati for generous assistance.

(6) H. Gilman and F. Schulze, THIS JOURNAL, **47**, 2002 (1925).
(7) O. Hinsberg, *Ann.*, **265**, 178 (1891).

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Steroid Mercaptols. II[1]

BY H. HAUPTMANN AND M. MOURA CAMPOS

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Some years ago[1] it was found that 7- and 12-ketosteroids form mercaptols only with dithiols, whereas the carbonyl groups in the 3-, 16[2] and 17-positions react also with monothiols. Recently, we examined cholestanol-3-one-6, whose keto group is generally more reactive than those in the 7- and 12-positions.[3] However, in the mercaptol formation under the usual conditions cholestanol-3-one-6 behaves in the same manner as the 7- and 12-ketosteroids in that it does not form a mercaptol with ethanethiol but reacts with ethanedithiol.

The 11-ketosteroids are known for their low reactivity. Accordingly ethyl 11-keto-3-hydroxyetiocholanate did not react with ethanedithiol[4] but was recovered almost completely. Similar observations have recently been made on 7,11-diketones derived from ergosterol and cholanic acid.[5]

A survey of the results obtained makes it obvious that all keto groups which form mercaptols with monothiols as well as with dithiols are in rings A and D, whereas those which give no mercaptols with monothiols are in rings B and C. Among these the 11-keto group shows a special behavior, since it is even inert to dithiols.

Studies on Stuart–Fischer–Hirschfelder models show that the 11-position is the only one in which a hemimercaptol cannot be constructed since there is not enough space around the carbon atom for both an alkylmercapto and a hydroxy group. This might explain why even with a dithiol no mercaptol is formed. However, more evidence will be necessary before a definite explanation of the behavior of the different keto groups can be given.

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Experimental

Treatment of Cholestanol-3-one-6 with Ethanethiol.—Dry hydrogen chloride was passed for two hours through a mixture of 450 mg. of cholestanol-3-one-6 and 4 ml. of ethanethiol cooled in an ice-bath. After standing overnight at room temperature, the mixture was kept in a vacuum desiccator over potassium hydroxide until all hydrogen chloride and ethanethiol had been removed. The residue was recrystallized twice from methanol, giving 400 mg., m.p. 142–144°, undepressed by admixture of starting material.

Reaction of Cholestanol-3-one-6 Acetate with Ethanedithiol.—Cholestanol-3-one-6 acetate (200 mg.) and 1.5 ml. of ethanedithiol were cooled in an ice-bath and treated with a stream of dry hydrogen chloride for two hours. After standing for several hours the reaction mixture was dissolved in ether, the ether solution washed with water, 5% sodium hydroxide and with water again, dried with calcium chloride and evaporated to dryness. The residue after several recrystallizations from acetone yielded the mercaptol, m.p. 148–151°, yield 190 mg. (80%).

Anal. Calcd. for $C_{31}H_{52}O_2S_2$: S, 12.31. Found: S, 12.13.

Treatment of 11-Keto-3-hydroxyetiocholanate with Ethanedithiol.—A stream of dry gaseous hydrogen chloride was allowed to pass through a mixture of 500 mg. of ethyl 11-keto-3-hydroxyetiocholanate and 2 ml. of ethanedithiol, cooled in an ice-bath. After 15 minutes the mixture was warmed to about 40° in order to dissolve the suspended ester. Passing of hydrogen chloride was continued at room temperature for half an hour, and 3 ml. of ethanedithiol was added when precipitation occurred again. After leaving the reaction mixture at room temperature for several hours the hydrogen chloride was removed in a vacuum desiccator over potassium hydroxide. The precipitate was separated by filtration, washed with petroleum ether and recrystal-

(1) H. Hauptmann, THIS JOURNAL, **69**, 562 (1947).
(2) M. N. Huffmann and M. H. Lott, *ibid.*, **69**, 1835 (1947).
(3) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949.
(4) This experiment was performed in the Converse Memorial Laboratory, Harvard University.
(5) H. Heusser, Y. Eichenberger, P. Kurath, H. R. Dallenbach and O. Jeger, *Helv. Chim. Acta*, **34**, 2106 (1951).