the next stage. For analysis it was recrystallized several times from acetic acid–ether, and then from ethanol–ether, m.p. 142–143°.

Anal. Calcd. for $C_6H_{14}ClNO_3$: C, 39.2; H, 7.6; N, 7.6. Found: C, 38.8; H, 7.4; N, 7.2.

N-γ-Methoxypropyl-N-nitrosoglycine. A solution of 4.6 g. of the foregoing hydrochloride in 15 ml. of water was cooled in ice, and 1.9 g. of sodium nitrite in 5.0 ml. of water added slowly with stirring. After 30 min. the clear solution was extracted with warm ethyl acetate. Evaporation of the dried extract *in vacuo* gave the nitroso compound as an oil which solidified on scratching, yield 2.8 g. (64%). It was recrystallized twice from ethyl acetate–petroleum ether, and formed slightly yellow needles, m.p. 70.5–71.5°.

Anal. Calcd. for $C_6H_{12}N_2O_4$: C, 40.9; H, 6.8; N, 15.9. Found: C, 41.1; H, 6.9; N, 15.8.

N-γ-Methoxypropylsydnone (III. n = 3, R = OCH_3). Treatment of 1.5 g. of the nitroso compound with 7.0 ml. of acetic anhydride in the usual way gave the sydnone as a slightly yellow oil, b.p. 164–165°/1 mm., yield 0.8 g. (60%). The compound solidified at −14°. Evidently slight decomposition occurred on distillation for the infrared spectrum contained a broad band at 2.86 μ, as well as the expected maxima at 3.20 μ (sydnone CH) and 5.76 μ (sydnone CO).

Anal. Calcd. for $C_6H_{10}N_2O_3$: C, 45.6; H, 6.3; N, 17.7. Found: C, 46.1; H, 6.4; N, 17.8.

N-β-Hydroxyethylglycine. Twenty one grams of *N-β*-hydroxyethylacetonitrile (prepared by the condensation of ethanolamine and hydroxyacetonitrile[15]) were refluxed for 2–3 hr. with 49.8 g. of barium hydroxide octahydrate in 160 ml. of water. The barium was removed by addition of a slight excess of sulfuric acid, and the filtered solution evaporated to small bulk and again filtered. Addition of ethanol precipitated the glycine as a colorless crystalline solid, m.p. 174–175°, yield 17.5 g. (70%). Kipriyanov and Kipriyanov[13] report m.p. 174–175°.

N-β-Hydroxyethyl-N-nitrosoglycine. A solution of 12.0 g. of sodium nitrite in 15 ml. of water was added slowly to an ice cold mixture of 17.5 g. of *N-β*-hydroxyethylglycine and 12.7 ml. of concd. hydrochloric acid in 10 ml. water. After keeping for 1–2 hr. at 0° the solution was extracted repeatedly with warm ethyl acetate. The nitroso compound was finally obtained as an oil which solidified on scratching. The product was washed with ether and dried, m.p. 73–75°, yield 8.3 g. (38%). Continuous extraction of the solution furnished more of the nitroso compound, but extensive resinification also occurred. For analysis the compound was recrystallized from ethyl acetate as almost colorless needles, m.p. 78.5–79.5°.

Anal. Calcd. for $C_4H_8N_2O_4$: C, 32.4; H, 5.4; N, 18.9. Found: C, 32.3; H, 5.7; N, 18.4.

The nitroso compound was also obtained in 41% yield by the action of nitrous fumes on an aqueous solution of *N-β*-hydroxyethylglycine, but the product was of inferior quality and very difficult to recrystallize.

N-β-Hydroxyethylsydnone (III. n = 2, R = OH). The foregoing nitroso compound (8.3 g.) was treated with 35 ml. of acetic anhydride for 4 days at room temperature, the mixture hydrolyzed with water, and then evaporated to dryness *in vacuo*. The residue was dissolved in ethyl acetate, and the solution shaken with concd. potassium carbonate solution, and dried over sodium sulfate. Evaporation gave the acetyl derivative (III. n = 2, R = $OCOCH_3$) as an oil which failed to solidify at −14°, and which decomposed extensively on distillation giving a black, tarry residue.

Treatment of the crude acetyl derivative with *p*-toluenesulfonyl chloride and pyridine failed to yield a *p*-toluenesulfonyl derivative (see below), thus indicating the absence of *N-β*-hydroxyethylsydnone in the product. The material also gave a strong Liebermann reaction, and probably contains the parent nitroso compound. In addition, it is possible that lactonization between the β-hydroxyl and the carboxyl groups may have occurred to some extent under the reaction conditions used.

A solution of 3 g. of the crude acetyl derivative (III. n = 2, R = $OCOCH_3$) in 20 ml. of water was refluxed with 9 g. of Zeo-Karb 225 acidic resin for 1 hr. The filtered solution was evaporated *in vacuo*, the residue dissolved in ethyl acetate and the dried solution evaporated. Crude *N-β*-hydroxyethylsydnone (III. n = 2, R = OH) was obtained as a viscous, almost colorless, oil. λ_{max}^{film} 2.94 (OH), 3.18 (sydnone CH), and 5.76 μ (sydnone CO).

An ice cold solution of the crude sydnone in 4 ml. of pyridine was treated dropwise with a solution of 2.7 g. of *p*-toluenesulfonyl chloride in pyridine. After 1 hr. the mixture was diluted with water, and the precipitated *p*-toluenesulfonyl derivative (III. n = 2, R = $OSO_2C_7H_7$) was collected and washed, yield 1.7 g. (27% overall), m.p. 118–120°. The compound formed colorless needles from ethanol, m.p. 120–121°. For analysis it was again recrystallized from ethanol, m.p. 120.5–121.5°. λ_{max}^{Nujol} 3.15 (sydnone CH), 5.73 (sydnone CO), 6.25 (benzene nucleus), 7.38 and 8.50 μ (sulfonate).

Anal. Calcd. for $C_{11}H_{12}N_2O_5S$: C, 46.5; H, 4.2; N, 9.9. Found: C, 46.4; H, 4.4; N, 9.7.

The *p*-toluenesulfonyl derivative was also obtained in 21% yield from crude *N-β*-hydroxyethylsydnone produced by selective hydrolysis of the acetyl derivative with Amberlite IRA-400 basic resin in water at room temperature for 12 hr.

N-γ-Bromopropylglycine hydrobromide. A mixture of 4.1 g. of *N-γ*-methoxypropylglycine hydrochloride, 40 ml. of 48% hydrobromic acid, and 100 ml. of glacial acetic acid was refluxed for 5 hr., and evaporated to dryness *in vacuo*. The residue was extracted with hot acetic acid and the filtered extract diluted with ethyl acetate. The hydrobromide separated as needles, and was recrystallized from ethanol–ether, m.p. 173.5–174.5°, yield 3.6 g. (59%). For analysis it was repeatedly recrystallized from ethanol–ether, but, nevertheless, failed to give very satisfactory analytical results.

Anal. Calcd. for $C_5H_{11}Br_2NO_2$: C, 21.7; H, 4.0; N, 5.1. Found: C, 22.6; H, 4.2; N, 4.5.

N-γ-Bromopropyl-N-nitrosoglycine. An ice-cooled solution of 3.4 g. of *N-γ*-bromopropylglycine hydrobromide in 9.0 ml. of water was treated dropwise with 1.0 g. of sodium nitrite in 4.0 ml. of water. The nitroso compound soon began to crystallize, and was collected after 30 min., and dried over phosphorus pentoxide *in vacuo*. It was recrystallized from ethyl acetate–petroleum ether, m.p. 87–88° dec., yield 1.1 g. (40%). The compound was unstable, and resinified readily. For analysis it was recrystallized from ether–petroleum ether when it formed colorless needles, m.p. 91.5–92.5°, which, however, slowly decomposed even on storage at 0°.

Anal. Calcd. for $C_5H_9BrN_2O_3$: C, 26.7; H, 4.0; N, 12.4. Found: C, 27.4; H, 4.1; N, 11.6.

Treatment of the nitroso compound with acetic anhydride in the cold for several days gave a red solution from which a dark brown, ether-insoluble, tacky material was isolated. This failed to solidify at −14°, and decomposed on heating. The infrared spectrum, however, contained distinct maxima at 3.20 and 5.79 μ indicating the probable presence of the sydnone nucleus.

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Halogen Reactivity in α-Fluoroanthraquinones

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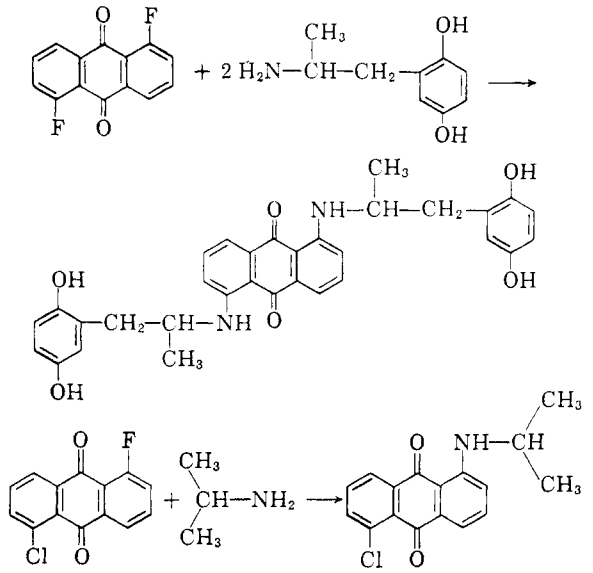
In searching for better "leaving groups" for displacement reactions in the anthraquinone system,

we have found that α-fluoroanthraquinones react with aliphatic amines under extremely mild conditions to give the corresponding aminoanthraquinones. This reactivity is particularly useful where the amine involved is heat-sensitive, or where the reactive α-nitroanthraquinones cannot be used because of redox reactions with substituents on the amine. Both of these conditions are successfully met in our preparation of 1,5-bis[β-(2′,5′-dihydroxyphenyl)α-methylethylamino] anthraquinone.



The selective replacement of fluorine in 1-chloro-5-fluoroanthraquinone[1] illustrates the difference in reactivity between the two halogens in these positions. Chlorine replacement does not occur to any appreciable extent below 100°.

EXPERIMENTAL

1,5-Bis(2′,5′-dihydroxyphenylisopropylamino)anthraquinone. A de-aerated mixture of 12.4 g. of 2-(2′-aminopropyl)-1,4-dihydroxybenzene hydrobromide (0.05*M*), 2.65 g. of anhydrous sodium carbonate (0.025*M*), and 50 ml. of pyridine was warmed until carbon dioxide evolution ceased. To this was added 1.3 g. (0.0053*M*) of 1,5-difluoroanthraquinone[2] and the mixture was stirred and heated on the steam bath for 4.5 hr. Most of the pyridine was blown off with nitrogen, then the reaction was quenched in 150 ml. of 3*N* hydrochloric acid. The precipitate was filtered, washed with warm water, and refiltered. Yield of magenta solid, m.p. 218–225°, λ = 526, 552, ε = 13,200, 11,800 (Methyl Cellosolve) was 2.3 g. (64.5%).

Anal. Calcd. for $C_{32}H_{30}N_2O_6$: C, 71.36; H, 5.61; N, 5.20. Found: C, 70.98; H, 5.50; N, 5.27.

1-Chloro-5-isopropylaminoanthraquinone. A mixture of 0.4 g. of 1-chloro-5-fluoroanthraquinone and 20 ml. of isopropylamine was stirred at room temperature overnight. Excess amine was evaporated in vacuum, and the residual red solid was crystallized from 30 ml. of ethanol to give 0.3 g. of red needles, m.p. 138–139° (56%).

(1) Prepared from 1-chloro-5-aminoanthraquinone *via* the Schiemann reaction, yellow crystals m.p. 201–203°, from ligroin.

(2) French Patent 1,250,130.

Anal. Calcd. for $C_{17}H_{14}ClNO_2$: Cl, 11.8; N, 4.7. Found: Cl, 12.3; N, 4.7.

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16-Hydroxylated Steroids. XXIII.[1] 21-Chloro-16α-hydroxycorticoids and Their 16α, 17α-Acetonides

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In this note we wish to record some observations regarding the effect of 16α,17α-acetonide formation on the biological activities of 21-chloro-16α-hydroxycorticoids.

It has been reported by the Squibb group[2] that 21-chloro-9α-fluoro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione in a liver glycogen assay was inactive at a dose level ten times the minimum effective dose of cortisone acetate. This was surprising in view of their observation that the activities of 21-fluorocorticoids lie between those of the corresponding 21-hydroxy and 21-deoxy derivatives. We have found that both 21-chloro-9α-fluoro-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione[3] (II) and 21-chloro-9α-fluoro-11β,16α,17α-trihydroxy-1,4-pregnadiene-3,20-dione (V) are inactive in a thymus involution assay at 30 times the minimum effective dose of hydrocortisone. However, the acetonides (VII, IX) of both 21-chloro-16α-hydroxy compounds were found to be highly active.[4] In Table I are given the biological activities of the 21-chloro compounds, along with those for 9α-fluoro-16α-hydroxyhydrocortisone (I) and triamcinolone (III) which have been included for comparative purposes.

The 21-chloro analog (VII) of 9α-fluoro-16α-hydroxyhydrocortisone acetonide apparently possesses a thymolytic activity which surpasses that of the parent 21-hydroxyacetonide (VI). It was also of interest to find that the 21-chloro-Δ^4-acetonide VII has a higher activity than the corresponding 21-chloro-$\Delta^{1,4}$-acetonide IX.

(1) Paper XXII, M. Heller, S. M. Stolar, and S. Bernstein, *J. Org. Chem.*, in process of publication.

(2) J. E. Herz, J. Fried, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **78**, 4812 (1956); J. Fried and A. Borman, *Vitamins and Hormones*, **16**, 303 (1958).

(3) S. Bernstein and R. H. Lenhard, *J. Am. Chem. Soc.*, **82**, 3680 (1960).

(4) A related finding has been reported by J. Fried (*Biological Activities of Steroids in Relation to Cancer*, ed. by G. Pincus and E. P. Vollmer, Chapt. 2, Academic Press, New York, 1960, page 9) with 12α-fluoro-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione with an activity of <0.1 × hydrocortisone whereas its acetonide had an activity of 10 × hydrocortisone.