trichloride and phosphorus oxychloride upon the quinazolone (III); yield nearly 50%. The preparation proved to be a rather tricky one. The quinazolone and the apparatus must be perfectly dry, the phosphorus oxychloride freshly distilled, and the temperature kept below 120°.

2-Phenethyl-4-methoxyquinazoline (V), from the above chloro derivative and sodium methylate, in absolute methanol solution; purified by crystallization from dilute (1:1) ethyl alcohol, it formed colorless needles, m. p. 58.5–59.8° (corr.), which were dried to constant weight and analyzed.

Anal. Calcd. for $C_{17}H_{16}ON_2$: C, 77.23; H, 6.10. Found: C, 77.09; H, 5.74.

Boiled with concentrated hydrochloric acid, this ether was hydrolyzed to 2-(β-phenethyl)-4-quinazolone.

2-(3',4'-Dimethoxystyryl)-4-quinazolone (II).—A mixture of 8.5 g. of veratraldehyde with 8 g. of 2-methyl-4-quinazolone was heated at 180–185°. After about two and one-half hours, the evolution of steam ceased. The mixture, liquid at first, partially solidified at the end of the first hour. The melt was dissolved in about 500 cc. of Cellosolve, 400 cc. of hot alcohol added, and the mixture cooled. The crystals which separated were removed, washed with a mixture of the same solvents, then with alcohol, and dried; yield, 10.9 g. of pale yellow crystals, m. p. 265–266°, with softening at about 264°. Purified by crystallization from Cellosolve, alcohol, or a mixture of the two, and decolorized by Norite, the compound was secured in fine pale yellow needles, m. p. 268–269° (corr.), nearly insoluble in glacial acetic acid, ethyl acetate, chloroform, acetone or benzene, in the cold and not much more soluble hot. The product was also difficultly soluble in hot ethyl alcohol, but dissolved more freely in hot isoamyl alcohol or in hot Cellosolve.

Anal. Calcd. for $C_{18}H_{16}O_3N_2$: C, 70.10; H, 5.23. Found: C, 70.57; H, 5.20.

2-Homoveratryl-4-quinazolone (III).—A suspension of 4 g. of the styryl derivative (II) in 500 cc. of 96% ethyl alcohol was heated under a reflux and reduced by the gradual addition of 150 g. of 3% sodium amalgam, after which the solution of the sodium salt was acidified and concentrated. The yield of crude product, m. p. 208.5–209.5° (corr.), was 92%. Recrystallized from ethyl alcohol and then from ethyl acetate, it formed long slender colorless needles, m. p. 209–210° (corr.).

Anal. Calcd. for $C_{18}H_{18}O_3N_2$: C, 69.64; H, 5.85. Found: C, 69.53; H, 5.51.

2-Homoveratryl-4-chloroquinazoline (IV) was prepared from the last-mentioned compound (III) by the action of a mixture of phosphorus oxychloride and phosphorus pentachloride. The crude product was obtained from ether solution in small pale yellow needles, m. p. 116–118°, easily soluble in ethyl alcohol or benzene, but only slightly in petroleum ether. Without further purification or analysis, this crude product was used direct for the synthesis of the

2-Homoveratryl-4-methoxyquinazoline (V), by dissolving it in absolute methanol and subjecting it to the action of sodium methylate for seventeen hours at room temperature. The yield of crude compound, m. p. 91–95°, from 0.55 g. of the chloroquinazoline was 0.42 g. Decolorized by Norite and crystallized from dilute (1:1) ethyl alcohol, it formed long slender flat colorless crystals, m. p. 96.3–97.3° (corr.).

Anal. Calcd. for $C_{19}H_{20}O_3N_2$: C, 70.33; H, 6.22. Found: C, 70.73; H, 6.58.

Boiled for a short time with concentrated hydrochloric acid, it was hydrolyzed to 2-homoveratryl-4-quinazolone.

Summary

1. Quinazoline derivatives have been synthesized, structurally analogous to the angostura alkaloids galiopine and galipine, for the purpose of comparing the physiological effects of the two series.

2. Incidentally, several other new quinazoline derivatives are described, and some old ones have been prepared by new methods.

NEW YORK, N. Y. RECEIVED JANUARY 21, 1935

[CONTRIBUTION FROM THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY]

A Study of Acid Degradation

BY MELVIN S. NEWMAN[1]

In degradation of α-bromo acid azides by the method of Curtius,[2] it has been found that, instead of amines, aldehydes and ketones are formed in accordance with the outline

$$R_1R_2CHCOOH \xrightarrow{(1)\ Br_2} R_1R_2CBrCOOH \xrightarrow{(2)\ SOCl_2} R_1R_2CBrCOCl \xrightarrow{(3)\ NaN_3} R_1R_2CBrCON_3 \xrightarrow{(4)\ \text{heat}} R_1R_2CBrNCO \xrightarrow{(5)\ HOH} R_1R_2CBrNH_2 \xrightarrow{(6)\ HOH} R_1COR_2$$

It is obvious that through this procedure aldehydes result from mono-substituted and ketones from di-substituted acetic acids.

This method of acid degradation had previously been suggested by von Braun,[3,4] but as the same scheme was independently evolved by the author at approximately the same time, Professor von Braun has graciously welcomed coöperation in this field.[5]

(1) National Research Council Fellow in Chemistry.

(2) Curtius, *J. prakt. Chem.*, [2] **50**, 275 (1894).

(3) Von Braun, *Petroleum Z.*, **28**, 50 (1932).

(4) Von Braun, *Ber.*, **67**, 218 (1934).

(5) Private communication.

Steps 1 and 2 were easily carried out by standard methods. Step 3 offered the greatest difficulties. Reactions 4, 5, and 6 were carried out without any attempt at isolation of intermediate products. Reaction 3 is greatly affected by the activity of the sodium azide, the nature of the acid chloride, and the conditions under which the two are brought into reaction.

In the cases of mono-substituted acetic acids, reaction 3 worked well in benzene, in acetic acid, or in the absence of any solvent. An advantage of working in acetic acid is that any sodium azide, even that totally inactive in benzene, may be used without decreasing the yield of aldehyde. When no solvent was used, active sodium azide gave slightly better yields than inactive.

In the cases of di-substituted acetic acids, reaction 3 took place very slowly in benzene. The sodium azide reacted to a large extent with the bromine to form sodium bromide, whereas in the case of reactions complete after ten minutes, less than 10% of sodium bromide was formed. When pyridine was used as a solvent[4] the yields were better than in the case of benzene, but not as good as when no solvent was used. However, pyridine was shown to exert a chemical action on α-bromo di-substituted actyl chlorides, removing the elements of hydrogen bromide. The unsaturated acid chlorides thus formed reacted with sodium azide to yield ketones, as follows

$$RCH_2CR'BrCOCl \xrightarrow{C_6H_5N} RCH{=}CR'COCl \xrightarrow{NaN_3}$$
$$[RCH{=}CR'CON_3] \xrightarrow{\text{heat}} [RCH{=}CR'NCO] \xrightarrow{HOH} RCH_2COR'$$

Although none of the isocyanate assumed to be formed in step 4 was isolated in pure form from the reaction between α-bromophenylacetyl chloride and sodium azide, a mixture of α-bromobenzyl isocyanate with a little unchanged acid chloride was obtained. The presence of the former was established in two experiments: on hydrolysis with dilute acid, carbon dioxide was evolved and over 90% of benzaldehyde was isolated; on reaction with alcohol, hydrogen bromide, benzaldehyde, and benzylidene diurethan[6] were formed.

$$C_6H_5CHBrNCO \xrightarrow{C_2H_5OH}$$
$$C_6H_5CHBrNHCOOC_2H_5 \xrightarrow{-HBr} [C_6H_5CH{=}NCOOC_2H_5]$$
$$2[C_6H_5CH{=}NCOOC_2H_5] \xrightarrow{HOH}$$
$$C_6H_5CHO + C_6H_5CH(NHCOOC_2H_5)_2$$

(6) Bischoff, *Ber.*, **7**, 634 (1874); Lehmann, *ibid.*, **34**, 370 (1901).

Since the proposed method of acid degradation was intended primarily for determination of structure in the naphthenic acid series, it was deemed important[5] to determine whether rearrangement of the cyclic structure occurs in the cases of α-bromocyclopentylacetyl chloride and α-bromohexahydrobenzoyl chloride. It was determined that pure cyclopentylmethanal and cyclohexanone were formed, respectively, no rearrangement occurring.

Experimental

α-Bromocyclopentylacetic Acid.—Ethyl cyclopentylidenecyanoacetate, made from cyclopentanone and ethyl cyanoacetate[7] with diethylamine as catalyst, was converted through ethyl cyclopentylcyanoacetate[8] to cyclopentylmalonic acid. This was brominated in dry ether and decarboxylated to α-bromocyclopentylacetic acid, m. p. 48–50°, in 50–60% yield (calcd. from cyclopentanone). The other bromo acids were prepared, in 85–95% yields, by the method of Hell, Volhard and Zelinsky, in all-glass equipment.[9] The acids were converted into acid chlorides in yields of 90–95%.

TABLE I

PHYSICAL CONSTANTS OF α-BROMO ACIDS AND α-BROMO ACID CHLORIDES

Parent acid	α-Bromo acid M. p., °C.	α-Bromo acid B. p. at 3–4 mm., °C.	α-Bromo acid chloride B. p., °C.
Phenylacetic	...	.....	123–126 at 17–8 mm.
Cyclopentylacetic	48–50	128–130	98–100 at 12–3 mm.
Hexahydrobenzoic	58–59	130–132	95– 96 at 3–4 mm.
Palmitic	50–51	.....	165–168 at 3–4 mm.
n-Heptylic	...	130–132	80– 82 at 3–4 mm.
Diethylacetic	...	68– 72	68– 72 at 10–2 mm.

Preparation of Active Sodium Azide.—Sodium azide was prepared according to Thiele,[10] but certain precautions were taken in order to obtain uniformly active material. Ethyl, isopropyl, and isoamyl nitrites, prepared according to Noyes,[11] were used and were distilled immediately before use. The reaction between the ethereal-nitrite and sodium methylate–hydrazine solution was started at −5 to −10° and maintained at this temperature with frequent vigorous shaking until a homogeneous solution resulted (about two hours). The preparation was completed by standing at 0° for at least five hours. The activity of sodium azide thus prepared remained unimpaired for several months when well protected from moisture. Sodium azide activated by the method of Nelles[12] was not used because of marked variations in the activity of different preparations. The activity of the sodium azide was determined by running a test reaction of the azide in question with α-bromophenylacetyl chloride in benzene and measuring the nitrogen evolved after heating for ten minutes on the steam-bath. When tested by this method, sodium

(7) Harding and Haworth, *J. Chem. Soc.*, **97**, 487 (1910).
(8) Vogel, *ibid.*, **115**, 2010 (1928).
(9) For α-bromodiethylacetic acid see Rosenmund, *Ber.*, **42**, 4472 (1909).
(10) Thiele, *ibid.*, **41**, 2681 (1908).
(11) Noyes, THIS JOURNAL, **55**, 3888 (1933).
(12) Nelles, *Ber.*, **65**, 1345 (1932).

azide (Nelles[12]) gave 50–90% of the calculated nitrogen; azide prepared as above always gave 90–95% nitrogen.

Reaction of Acid Chlorides with Sodium Azide in Inert Solvents.—For these reactions, the reaction flask was fitted with a ground-in reflux condenser connected through its upper end with an azotometer. To a known amount of acid chloride in about ten times its weight of solvent, a slight excess of sodium azide was added in one portion. The flask was then heated on the steam-bath until no more gas was evolved (usually ten minutes). Waiting for various lengths of time before heating did not increase the yields. The solvent was removed under reduced pressure, the residue heated with dilute hydrochloric acid for one-quarter to one-half hour, and the carbonyl compound isolated and identified by making a suitable derivative.

Reaction of Acid Chlorides with Sodium Azide in Acetic Acid.—These reactions were carried out by adding a 50% excess of sodium azide in small portions to a cooled solution of the acid chloride in 10–20 times its weight of glacial acetic acid. After standing at room temperature for one-half hour, the mixture was warmed cautiously until the evolution of gas became lively, when it was *quickly* cooled in ice water. The flask was then alternately heated and cooled in the same way several times and finally heated for ten minutes. When this procedure was not followed the reaction mixture would boil out of the reflux condenser when first heated.

Reaction of Acid Chlorides with Sodium Azide without Solvents.—A small excess of sodium azide was added in small portions to the acid chloride at 0°. After standing at room temperature for one day, the mixture was warmed slowly with dilute hydrochloric acid (hood) and the carbonyl compound isolated.

TABLE II

REACTIONS OF α-BROMO ACID CHLORIDES WITH SODIUM AZIDE

Active sodium azide prepared as described was used in every experiment unless otherwise noted.

Parent acid	% N_2 coll.	Carbonyl isolated, %	Conditions
Phenylacetic	95	80	Benzene
Phenylacetic	93	73	Toluene
Phenylacetic	49	39	Acetone
Phenylacetic	..	51	Aqueous acetone
Phenylacetic	44	32	Ether
Phenylacetic	..	79	Acetic acid
Phenylacetic	..	78	Acetic acid + commercial NaN_3
Phenylacetic	..	61	No solv., heated 1 hr. at 100°[a]
Phenylacetic	..	60	No solv., heated 1 hr. at 150°[a]
Phenylacetic	..	67	No solv., heated 1 hr. at 100°
Cyclopentylacetic	90	53	Benzene
Cyclopentylacetic	..	54	No solvent[b]
Cyclopentylacetic	..	53	Acetic acid[a]
n-Heptylic	90	62	Benzene
n-Heptylic	..	62	No solvent
n-Heptylic	..	50	Acetic acid[a]
Palmitic	65[c]	59[d]	Benzene
Palmitic	..	31	No solvent
Palmitic	..	27	Acetic acid[a]
Hexahydrobenzoic	..	10	Benzene
Hexahydrobenzoic	80	20	Refluxed 6 hrs. in benzene
Hexahydrobenzoic	80	41	Pyridine
Hexahydrobenzoic	..	32	Acetic acid
Hexahydrobenzoic	..	44	No solvent
Diethylacetic	..	..	Benzene
Diethylacetic	53	31	Pyridine
Diethylacetic	..	35	No solvent

[a] Sodium azide (Thiele) but inactive. [b] Carbonyl compound obtained mostly as polymer. [c] Not exact as copious frothing prevented accurate measurement. [d] Corrected value for unchanged α-bromopalmitic acid recovered.

Identification of Products.—Benzaldehyde was identified as its phenylhydrazone, m. p. and mixed m. p. 156°; cyclohexanone, *n*-hexanal, and pentadecanal as their 2,4-dinitrophenylhydrazones, m. p., respectively, 157–158, 106–107, and 106–107°. The last, a new compound, crystallizes from pyridine–alcohol in small yellow prisms.

Anal. Calcd. for $C_{21}H_{34}O_4N_4$: N, 13.79. Found: N, 13.85.

Diethyl ketone was identified as its semicarbazone, m. p. and mixed m. p. 137–138°, and cyclopentylmethanal as its dimedon[13] condensation product, a new compound crystallizing from dilute alcohol in shiny plates, m. p. and mixed m. p. 162–163°.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.28; H, 8.96. Found: C, 73.40; H, 8.85.

This compound was converted into the anhydride,[13] m. p. and mixed m. p. 157–158°.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.14; H, 8.84. Found: C, 77.30; H, 8.72.

Preparation of Cyclopentylmethanal.—Cyclopentanone was condensed with ethyl chloroacetate by the method of Darzens.[14] The yield of glycide-ester, b. p. 90–95° at 3–4 mm. was 41%.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.49; H, 8.30. Found: C, 63.49; H, 8.11.

The sodium salt was obtained by Claisen's[15] method in 95% yield. On steam distillation of the acidified aqueous solution of the sodium salt, cyclopentylmethanal, b. p. 135–136°, was obtained in poor yield.

Analysis of Sodium Salts.—The sodium salts obtained from the reactions of acid chlorides with sodium azide consisted of a mixture of sodium chloride, bromide and azide. After destroying the azide by heating with acid in the hood, the bromine was determined by a standard method. The salts obtained from the reactions of α-bromophenylacetyl chloride, α-bromo-*n*-heptoyl chloride, and α-bromocyclopentylacetyl chlorides with sodium azide analyzed for 10.0, 9.4 and 9.6% sodium bromide, respectively. Those salts from the reaction of α-bromohexahydrobenzoyl chloride contained 60.4% sodium bromide (six hour run).

Action of Pyridine on α-Bromo Di-substituted Acetyl Chlorides.—To 20 cc. of pyridine at 0°, 3.5 g. of α-bromohexahydrobenzoyl chloride was added slowly. The mixture was heated on the steam-bath for ten minutes, cooled and 20 cc. of absolute alcohol was added. After standing at room temperature for one day, the reaction mixture was poured into dilute hydrochloric acid. The product, isolated by ether extraction, weighed 1.8 g. and proved to be almost pure ethyl tetrahydrobenzoate. By analysis, less than 0.2% of bromine was present. After distillation *in vacuo* the ester was analyzed.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.08; H, 9.16. Found: C, 70.26; H, 8.77.

(13) Houben, "Methoden der org. Chem.," 3d ed., Verlag Georg Thieme, Leipzig, 1930, p. 571.

(14) Darzens and Lefébure, *Compt. rend.*, **142**, 714 (1906).

(15) Claisen, *Ber.*, **38**, 699 (1905).

The same process was repeated using 3.33 g. of α-bromodiethylacetyl chloride. In this case the removal of hydrogen bromide was not as complete, the product, 2.1 g., obtained analyzing for 29.75% bromine, 35.85% being the theoretical for $C_8H_{15}O_2Br$.

Reaction of Unsaturated Acid Chlorides with Sodium Azide.—The unsaturated acids were prepared from α-bromo esters by heating with dimethylaniline at 175–180° for one to two hours and subsequent hydrolysis. Thus prepared, tetrahydrobenzoyl chloride, b. p. 90–2° at 14–15 mm., and α-ethylcrotonyl chloride, b. p. 54–57° at 14–15 mm., reacted with sodium azide in benzene to yield cyclohexanone (60%) and diethyl ketone (56%).

Examination of Cyclopentylmethanal and Cyclohexanone for Rearrangement Products.—The cyclopentylmethanal from several runs was united and distilled. One gram of the highest boiling fraction, 136–137°, was dissolved in acetone and an excess of finely powdered potassium permanganate was added. After standing at room temperature for three days, the manganese dioxide was removed and the neutral fraction extracted with ether. Since no appreciable residue was obtained on removal of the ether, cyclohexanone was proved absent in the original mixture, for when an authentic mixture of cyclopentylmethanal and cyclohexanone was treated in the same way, cyclohexanone was demonstrable.

The cyclohexanone from several runs was united and distilled. One gram of the lowest boiling fraction was tested for the presence of aldehyde. No color developed with fuchsin-sulfur dioxide reagent and no dimedon condensation product was obtained.

Isolation of α-Bromobenzyl Isocyanate.—Thirty grams of α-bromophenylacetyl chloride in 100 cc. of benzene was treated with 9 g. of sodium azide. After heating for ten minutes, the benzene was removed *in vacuo* and the residue distilled. The second fraction, b. p. 110–120° at 18–19 mm., was redistilled and the portion of b. p. 114–116° at 18–19 mm. analyzed.

Anal. Calcd. for C_8H_6ONBr: N, 6.61; Br, 37.70. Found: N, 5.63; Br, 39.85.

On hydrolysis with dilute acid, 3.84 g. yielded 1.74 g. (90%) of benzaldehyde.

Formation of Benzylidene Diurethan.—The α-bromobenzyl isocyanate was dissolved in dry ether and added slowly to absolute alcohol. The ether was removed with a current of dry air and the alcohol in a vacuum desiccator. The residue was triturated with hexane and the crystals filtered and washed with cold water and alcohol to remove all traces of hydrobromic acid. The product was recrystallized from alcohol by the addition of water and was identical with benzylidene diurethan, m. p. and mixed m. p. 179–180°.[6]

Anal. Calcd. for $C_{18}H_{18}O_4N_2$: C, 58.61; H, 6.82; N, 10.53. Found: C, 58.65; H, 6.9; N, 10.51.

The author takes this opportunity to thank Dr. H. T. Clarke for his interest in this work, and Mr. W. Saschek for the microanalyses.

Summary

1. Application of the Curtius rearrangement to α-bromo acids has been shown to lead to the formation of carbonyl compounds.

2. α-Bromocyclopentylacetic acid and α-bromohexahydrobenzoic acid yielded cyclopentylmethanal and cyclohexanone, respectively, no rearrangement of the cyclic structure taking place.

3. The preparation of uniformly active sodium azide is described.

NEW YORK, N. Y. RECEIVED JANUARY 21, 1935

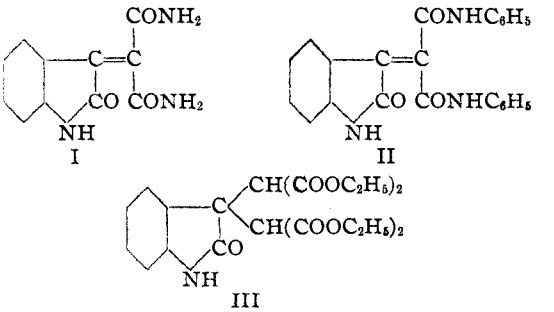
[CONTRIBUTION FROM THE NICHOLS LABORATORY OF NEW YORK UNIVERSITY AND THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

Condensation Reactions of Cyclic Ketones. III. Oxindole-malonic Acid Derivatives

BY H. G. LINDWALL AND ARTHUR J. HILL

The previous paper[1] of this series dealt with the behavior on hydrolysis of the reduced products of the indigoids derived from the condensation of isatin with diketopiperazine and hydantoin; quinolones were obtained. This investigation involves further syntheses of oxindole derivatives for the purpose of studying their hydrolytic products.

Isatin has been condensed with ammonium malonate, malonamide, and malonanilide by the use of ammonia as a catalyst and with diethyl malonate under the influence of diethylamine. The characteristics of the ammonium malonate product have been studied. Malonamide and malonanilide yield 3-(diformamido)-methyleneoxindole (I) and 3-(diformanilido)-methyleneoxindole (II), respectively. Diethylmalonate



(1) Hill, Schultz and Lindwall, THIS JOURNAL, **52**, 769 (1930).