double beam operation and matched cells. The instrument was operated according to the manufacturer's recommendations. The data obtained are listed in Table I.

Ultraviolet Spectra. The ultraviolet spectra were determined using a Cary Model 14 double-beam recording instrument. The solutions were freshly prepared in 95% ethanol and kept in the dark until used. Concentrations were 10^{-3} and 10^{-4} molar. Matched cells were used. The instrument was operated according to manufacturer's recommendations. Extinction coefficients were determined in the usual manner (ref. 11, p. 181). The data obtained are listed in Table II.

Fading absorbance was noted in alcohol solutions of II and III on standing. The 3430 Å band of II decreased to 20% of its initial intensity in 17 hr. on standing in the dark at room temperature. The 3400 Å band of III decreased to 76% of its initial intensity on standing 17 hr. in the dark at room temperature.

Acknowledgment. This work was supported in part by a Summer Faculty Research Grant from E. I. du Pont de Nemours and Company, which is gratefully acknowledged.

The purchase of the infrared spectrophotometer used in this study was made possible by a grant from the National Science Foundation.

IOWA CITY, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

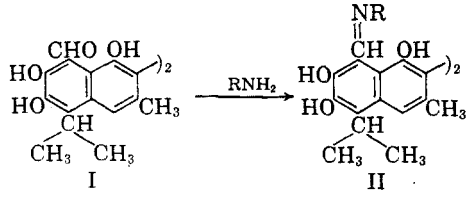
Some New Anil Derivatives of Gossypol[1]

PEGGY W. ALLEY AND DAVID A. SHIRLEY

Received May 25, 1959

The scope of the reaction of Schiff base (anil) formation between gossypol and primary amines has been investigated. Seventeen primary amines of widely varying types were reacted with gossypol and the anil derivates isolated.

It has recently been demonstrated[2] in this laboratory that aliphatic amines form stable derivatives (II) of gossypol (I) analogous to the long known[3] dianilinogossypol (II,R=phenyl) and related aromatic anil derivatives.[4]



I II

We have prepared a variety of new anil derivatives of gossypol in order to determine the scope of the reaction and to obtain potentially useful gossypol derivatives. The amines selected for anil formation with gossypol were in general of the following types: (1) amines containing other functional groups which should permit further reactions of the gossypol anils, (2) physiologically active amines which might impart biological activity to the anil formed, (3) azo dyes containing amino groups, and (4) amino acid and dipeptide esters.

Of particular interest were the anils with the methyl esters of lysine, glycine and the dipeptide glycylglycine. It has been proposed that gossypol becomes chemically bound with protein during the processing of cottonseed meal.[5] The site of the binding is the free amino groups present in the cottonseed protein and the terminal amino groups of lysine has seemed to be a likely spot. While the preparation of these amino acid ester anils does not offer any direct evidence for the site of binding, it demonstates that moderately stable anils of this type may be formed. The reaction product of lysine methyl ester and gossypol contained a 1:1 ratio of the two reactants indicating either anil formation at both amino groups in the lysine molecule (resulting in a polymeric type material) or reaction at only one carbonyl site in the gossypol molecule with one amine function (probably the terminal amino group[6]) in the lysine methyl ester molecule. The analytical data on the product agree more closely with the latter possibility.

The normal product (II,R=CH_2COOCH_3) was obtained from the reaction of gossypol and glycine methyl ester. The product from the reaction of glycylglycine methyl ester and gossypol was identical (analytical data and infrared spectra comparison) with that from glycine methyl ester and gossypol. Hydrolysis of the dipeptide apparently occurred during its liberation from the hydrochloride or during the anil formation.

Gossypol acetic acid complex[7] was used for all reactions. The yields of anils were generally quite satisfactory as indicated in Table I.

---

(1) A report of work conducted under contract with the U. S. Department of Agriculture and authorized by the Research and Marketing Act. The contract is being supervised by the Southern Utilization Research and Development Division of the Agricultural Research Service.

(2) D. A. Shirley and W. C. Sheehan, *J. Org. Chem.*, **21**, 251 (1956).

(3) F. E. Carruth, *J. Am. Chem. Soc.*, **40**, 647 (1918).

(4) J. M. Dechary and L. E. Brown, *J. Am. Oil Chemists Soc.*, **33**, 76 (1956).

(5) E. P. Clark, *J. Biol. Chem.*, **76**, 229–235 (1928).

(6) B. Witkop and T. W. Beiler, *J. Am. Chem. Soc.*, **76**, 5589 (1954).

(7) Supplied by Southern Utilization Research and Development Division Laboratory, Agricultural Research Service.

TABLE I

NEW ANIL DERIVATIVES OF GOSSYPOL

Compound (R in II)	Molecular Formula	M.P., °C.	Yield, %	Recrystallization Solvent	Analyses					
					Calcd.			Found		
					C	H	N	C	H	N
2-Ethylhexylamine	$C_{46}H_{68}N_2O_6$	200°–201°	78	ethanol-benzene	74.15	9.20	3.76	74.15 74.31	8.99 8.87	3.94 4.07
β-Phenylethylamine	$C_{46}H_{48}N_2O_6$	dec. >225°	91	isopropyl alcohol–benzene	76.22	6.67	3.87	76.37 76.07	6.51 6.71	3.74 3.62
Allylamine	$C_{36}H_{40}N_2O_6$	dec. >200°	97	benzene-ethanol	72.46	6.76	4.70	72.51 72.60	6.53 6.92	4.62 4.47
p-Aminoacetophenone	$C_{46}H_{44}N_2O_8$	dec. >200°	100	.....	73.38	5.89	3.72	73.16	6.08	3.99
N,N-Diethylethylenediamine	$C_{42}H_{58}N_4O$	dec. >200°	72	benzene–isopropyl alcohol	70.6	8.13	7.85	70.00	8.18	7.62
N,N-Dimethyl-1,3-propanediamine	$C_{40}H_{54}N_4O_6$	200° (dec.)	88	benzene-ethanol	69.94	7.92	8.16	69.53 69.32	7.90 7.68	8.29
p-Aminohippuric[a] acid	$C_{48}H_{46}N_4O_{12}$	dec. >200°	80	.....	66.19	5.34	6.43	64.36 64.10	5.84 5.78	5.72 5.92
p-Aminobenzene-[a] sulfonamide	$C_{42}H_{42}N_4O_{10}S_2$	dec. >200°	77	.....	61.26	5.13	6.78	59.63 59.43	5.41 5.53	7.05 6.92
p-Aminoazo-[b] benzene	$C_{54}H_{48}N_6O_6$	280° (dec.)	81	.....	73.95	5.51	9.58	72.93 72.90	5.62 5.54	9.15 9.22
4-*o*-Tolyazo-*o*-[b] toluidine	$C_{58}H_{56}N_6O_6$	270°–273° (dec.)	87	.....	74.68	6.05	9.00	73.10 73.10	5.75 5.86	7.35 7.54
p-Aminobenzoic[a] acid, *n*-butyl-ester	$C_{52}H_{56}N_2O_{10}$	200°–210°, resolidified 230° (dec.)	100	.....	71.86	6.50	3.22	71.15 71.49	6.52 6.52	3.20 3.02
Aminoacetal	$C_{42}H_{58}N_2O_{10}$	207° (dec.)	77	benzene–isopropyl alcohol	67.18	7.79	3.74	67.13 67.08	7.49 7.64	3.88 3.56
p-Bromobenzylamine	$C_{44}H_{42}Br_2N_2O_6$	251°–254° (dec.)	100	chloroform-methanol	61.83	4.96	3.28	62.34 62.43	4.81 5.00	3.08 3.24
p-Nitrobenzylamine	$C_{44}H_{42}N_4O_{10}$	234° (dec.)	97	chloroform-methanol	67.17	5.38	7.12	67.05 66.80	5.61 5.19	7.10 7.23
p-Chlorobenzylamine	$C_{44}H_{42}Cl_2N_2O_6$	236.5°–237.5° (dec.)	94	benzene–ethanol	69.00	5.53	3.66	69.31 68.93	5.67 5.50	3.55 3.53
Glycine methyl ester	$C_{36}H_{40}N_2O_{10}$	205°–210° (dec.)	9	isopropyl alcohol	65.44	6.10	4.24	64.50 64.65	6.23 6.31	3.94 3.96

[a] Insoluble in ordinary organic solvents. [b] Unstable in ordinary organic solvents.

EXPERIMENTAL[8]

Diallylaminogossypol A solution of 1.00 g. (0.00173 mole) of gossypol acetic acid complex[7] in 70 ml. of isopropyl alcohol was heated to boiling and a solution of 2 ml. (excess) of allylamine in 20 ml. of isopropyl alcohol was added. The solution was boiled for several minutes and allowed to stand overnight at 5°. The precipitated yellow crystalline solid was separated by filtration, washed with fresh isopropyl alcohol and dried. The yield was 1.00 g. or 97%. A sample for analysis was recrystallized from a benzene and ethanol mixture.

Anal. Calcd. for $C_{36}H_{40}N_2O_6$: C, 72.46; H, 6.76; N, 4.70. Found: C, 72.51, 72.60; H, 6.53, 6.92; N, 4.62, 4.47.

The compounds listed in Table I were prepared in general accordance with the above procedure except that recrystallization solvents varied as shown. Some of the anils could not be recrystallized because of either solubility difficulties or instability in solution. In cases where recrystallization was not possible, part of the analytical results usually differed somewhat from the calculated values.

(8) Microanalyses by Weiler and Strauss, Oxford, England, and Galbraith Microanalytical Laboratories, Knoxville, Tennessee. All melting points were taken on a Kofler Hot Stage Microscope.

Reaction of gossypol with L-lysine methyl ester. Two and one half grams of L-lysine methyl ester dihydrochloride was mixed with an equal weight of potassium carbonate and slurried in 25 ml. of isopropyl alcohol. Enough water was added to bring the solids into solution, and the resulting solution was extracted with equal volumes of ether. The combined ethereal extracts were added to a hot solution of 1.00 g (0.00173 mole) of gossypol acetic acid in 70 ml. of isopropyl alcohol, and the solution was heated on the steam bath until the ether had evaporated. The resulting solution was filtered and the filtrate placed overnight in the cold room. A bright yellow solid precipitated and was separated by filtration, washed with fresh isopropyl alcohol and dried. The crude product weighed 0.60 g. (43% of theory for 2:1 ratio; 53% for 1:1 ratio.) During an attempted recrystallization of the product from isopropyl alcohol, the material became gummy on contact with the hot solvent. The gum was partially brought into solution by the addition of benzene. The mixture was filtered from 300 mg. of insoluble material. On cooling the filtrate, there was precipitated 0.10 g. of yellow solid product.

Anal. Calcd. for $C_{44}H_{60}N_4O_{10}$ (2:1 ratio): C, 65.65; H, 7.51, N, 6.96. Calcd. for $C_{37}H_{44}N_2O_9$ (1:1 ratio): C, 67.25; H, 6.71; N, 4.24. Calcd. for $C_{37}H_{42}N_2O_8$ (1:1 ratio, repeating unit of polymer product): C, 69.14; H, 6.59; N, 4.36. Found:

C, 67.93, 67.80; H, 6.45, 6.66; N, 4.33, 4.55. The ratios in the parantheses represent the molar ratio of L-lysine methyl ester to gossypol in anil product molecule.

The infrared spectrum (KBr disc) of the product showed medium adsorption at 5.72 μ (ester carbonyl) and strong adsorption at 6.19 μ. The band at 6.19 μ is characteristic of the >CH=N linkage in gossypol anils. The anils from gossypol and the amines listed show adsorption in this region: aniline (6.20 μ), *p*-aminohippuric acid (6.17 μ), β-diethylaminoethylamine (6.20 μ), and glycine methyl ester (6.18 μ). Thus the data support strongly the formation of an anil linkage in the gossypol–lysine methyl ester reaction and the analytical data indicate a product containing one molecule of each.

KNOXVILLE, TENN.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Preparation of Substituted Cyclopropanes Containing Aldehyde and Ketone Groups

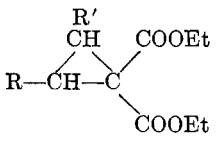
DONALD T. WARNER

Received May 25, 1959

The reaction of acrolein with ethyl bromomalonate in the presence of a molar quantity of sodium ethoxide produces diethyl 2-formylcyclopropane-1,1-dicarboxylate as the main product. Similar reactions of ethyl bromomalonate with crotonaldehyde and methyl vinyl ketone also produce the corresponding substituted cyclopropane compounds. These compounds show the characteristic absorption bands for cyclopropanes in the infrared and near infrared regions of the spectrum.

In a previous publication,[1] the reaction of acrolein with ethyl bromomalonate was described briefly. In the presence of a molar quantity of sodium ethoxide, the reaction product was an aldehyde which contained no bromine. At that time, the reaction product was presumed to be 4,4-dicarbethoxy-3-butenal, resulting from the elimination of hydrogen bromide after the 1,4-addition of bromomalonate to acrolein. The facile hydrogenation of the product to γ,γ-dicarbethoxybutyraldehyde was presented as evidence for the proposed structure.

In a subsequent discussion of this reaction with Professor M. S. Newman, he suggested that the observed dehydrohalogenation might also lead to a cyclopropane structure. If this ring were formed in the acrolein-bromomalonate reaction, the resulting product would be diethyl 2-formylcyclopropane-1,1-dicarboxylate (I) instead of the previously proposed 4,4-dicarbethoxy-3-butenal. The recent disclosure of a cyclopropane ring in the amino acid, hypoglycin,[2a-f] and other natural products has suggested the desirability of preparing certain cyclopropane compounds with aldehydo substituents as intermediates for the probable synthesis of such products. We have therefore prepared additional quantities of the acrolein-bromomalonate intermediate and examined it for the presence of a cyclopropane structure such as I by all of the available methods.



I. R = CHO, R′ = H
II. R = CH_3CO, R′ = H
III. R = CHO, R′ = CH_3

As an initial investigation of the compound, samples were submitted for spectral analysis. The infrared spectrum showed strong absorption maxima at 1002–1015 cm.$^{-1}$, 856 cm.$^{-1}$, and a very definite C—H stretching band at 3070 cm.$^{-1}$ All of these features have been assigned to the cyclopropane ring in the infrared region.[3a-d] The compound was also examined in the near infrared in accordance with the recent observations of Washburn and Mahoney,[3d] and it showed absorptions at about 1.65 μ (6061 cm.$^{-1}$) and 2.25 μ (4444 cm.$^{-1}$) characteristic of cyclopropanes. Although the recent study of Allen and his co-workers[4] would indicate that the assignment of structure for probable cyclopropane compounds on the sole basis of infrared spectral data can be hazardous, in this instance the ultraviolet spectrum also showed the absence of a conjugated carbon-carbon double bond which would be present in 4,4-dicarbethoxy-3-butenal. In view of the rather limited number of possibilities for the present compound, the spectral evidence strongly

(1) D. T. Warner and O. A. Moe, *J. Am. Chem. Soc.*, **70**, 3470 (1948). This reaction is also the subject matter of U. S. Patent **2,540,054**, Jan. 30, 1951.

(2) (a) S. Wilkinson, *Chem. & Ind. (London)*, 7 (1958). (b) C. V. Holt and W. Leppla, *Angew. Chem.*, **70**, 25 (1958). (c) J. A. Carbon, W. B. Martin, and L. R. Swett, *J. Am. Chem. Soc.*, **80**, 1002, (1958). (d) R. S. DeRopp, J. C. Van Meter, E. C. DeRenzo, K. W. McKerns, C. Pidacks, P. H. Bell, E. F. Ullman, S. R. Safir, W. J. Fanshawe, and S. B. Davis, *J. Am. Chem. Soc.*, **80**, 1004 (1958). (e) E. V. Ellington, C. H. Hassell, and J. R. Plimmer, *Chem. & Ind. (London)*, 329 (1958). (f) H. V. Anderson, J. L. Johnson, J. W. Nelson, E. C. Olson, M. E. Speeter, and J. J. Vavra, *Chem. & Ind. (London)*, 330 (1958).

(3) (a) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, New York, N. Y., 1954, pp. 27–8. (b) S. E. Wimberley and S. C. Bunce, *Anal. Chem.*, **24**, 623 (1952). (c) G. W. King, R. T. Armstrong, and L. Harris, *J. Am. Chem. Soc.*, **58**, 1580 (1936). (d) W. H. Washburn and M. J. Mahoney, *J. Am. Chem. Soc.*, **80**, 504 (1958).

(4) C. F. H. Allen, T. J. Davis, W. J. Humphlett, and D. W. Stewart, *J. Org. Chem.*, **22**, 1291 (1957).